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Global Stability in Epidemiological Models

by

C. Connell McCluskey

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Department of Mathematical and Statistical Sciences

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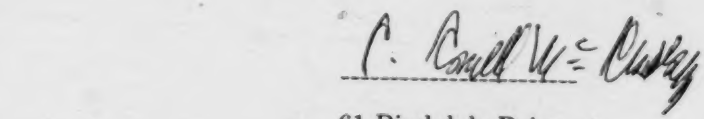

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The only thing I knew how to do, was to keep on keeping on.

- Bob Dylan

For the Mighty Fiona

Abstract

Theoretical concepts related to the stability of continuous dynamical systems are investigated. These concepts are then applied to various epidemiological models. A strategy is presented for showing stability of time-dependent linear systems. The strategy describes how to develop non-absolute norms which are designed to take advantage of both the signs and the magnitudes of the entries in the derivative matrix. Techniques, involving compound matrices, for the analysis of the asymptotic behaviour of a dynamical system are studied. A theorem which can be used to show that a boundary equilibrium is globally stable, is proven. A new technique for analyzing behaviour on an invariant manifold is presented. This involves characterizing all dynamical systems whose restriction to the manifold is the same as the restriction of the system which is under consideration. A test is given that can be used on a homogeneous differential equation in three variables to obtain information about the limiting behaviour of solutions. The method is applied to a general example which includes several epidemiological models.

Several systems are studied which model the interaction of an infectious disease and a gene that confers some protection from the disease. A model of differ-

ential infectivity is analyzed. A threshold parameter is calculated and the impact that it has on the dynamics is determined. Global stability is demonstrated for a subset of the parameter space. A model of staged progression and amelioration is presented. When the total population exceeds a certain threshold, there is a globally stable endemic equilibrium. When the total population is below the threshold, the disease-free equilibrium is globally stable. A second model of staged progression and amelioration is also studied. A threshold parameter is calculated and its implications for stability are demonstrated. Global stability is shown for a subset of the parameter space. An advance is made on the global stability problem for the MSEIR model. It is shown that, when present, the unique endemic equilibrium is globally stable if the proportion of the population in the exposed class at the endemic equilibrium is greater than the proportion in the passively immune class. Recommendations are given for future work related to various topics covered in the thesis. The recommendations are both mathematical and biological in nature.

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CHAPTER 1

Introduction

1.1 Mathematical Epidemiology

Mathematical epidemiology is concerned with modeling the spread of disease in a population. The aim is generally to understand the time course of the disease. In 1906 Hamer studied a discrete time model in an attempt to understand the recurrence of measles epidemics [19]. Ross, in 1911, formulated and analyzed a differential equation model of malaria [52]. Beginning in 1926, Kermack and McKendrick published important work in which they determined threshold behaviour for epidemic models showing that it was necessary for the density of susceptibles to exceed a critical value in order for an epidemic outbreak to occur [30]. More recently, mathematical epidemiology has grown dramatically. Recent models involve more complex behaviour including, for example, age structure [22], quarantine and gradual waning of the efficacy of a vaccine. A more detailed survey of the history of mathematical epidemiology is given by Hethcote in [22]. Today, mathematical models are used to guide health policy in several ways including vaccination strategies for childhood diseases [18, 22].

In constructing a model, it is necessary to clarify the assumptions, variables and parameters which are specific to the situation being modelled. By building multiple models based on different assumptions, it is possible to explore various viewpoints regarding disease control strategies. Analysis of models may suggest crucial information which needs to be collected. Another strength of models is that they can be used to identify trends and make forecasts.

Models can be classified as deterministic or stochastic. Deterministic models

treat the development of an epidemic in a population as a process which follows exact rules, often yielding precise predictions about the state of the disease in the future. Such models ignore the inherent role of chance in the spread of an infectious disease. Stochastic models incorporate randomness, providing a greater level of realism. The disadvantage of stochastic models is that the analysis is generally more difficult than the analysis of a similar deterministic model. A more detailed discussion of the strengths and limitations of epidemiological models is given by, for example, Hethcote and Van Ark in [23].

Some models take into account the spatial distribution of a population and describe the development of a disease as it diffuses through a region. Mathematically, this involves the use of partial differential equations. Delay differential equations and integral equations can be used to account for the fact that sometimes the change in the disease status of a population at a particular instant is affected by events at other times. For example, we may assume that after becoming infected with a disease, an individual does not become infectious until a fixed amount of time τ has passed. Thus, the rate of change in the number of infectious individuals at time t is a function of the disease status of the population at time $t - \tau$. Although more complicated models of this type are generally more realistic, they are more difficult to analyze. In particular, it is uncommon for global stability to be demonstrated for models which involve these more complex behaviours. It is often necessary to choose between the detail involved in the model and the conclusions that can be made based on the analysis.

In this thesis we deal with deterministic models involving ordinary differential equations. While not always allowing for the level of realism that other classes of models achieve, these models have value in the fact that they lend themselves more readily to detailed analysis. They are useful for policy-making decisions but less

effective in fitting data or in predicting the progress of a specific outbreak.

1.2 Compartment Models

In compartment models, the population is divided into n groups with sizes $X_1, \ldots, X_n \geq 0$. The differential equations which arise frequently take the form

$$X_j' = f_j(X) - X_j g_j(X) \tag{1.1}$$

for $j = 1, \ldots, n$, where f_j describes the flow of individuals into group j and g_j is the per capita rate at which individuals leave group j. Specific model assumptions further determine f_j and g_j. Diseases which have been modelled in this way include Human Immuno-deficiency Virus (HIV) [26, 27, 43], measles [1, 14, 21] and varicella [53].

An aspect of disease behaviour is often modelled without a particular disease being specified. A differential equation which models the population is found, taking into account assumptions such as waiting times in the various groups, contact patterns and the introduction or recruitment of new individuals into the population. Models of this type include the classic SIR, SEIR, and SIS models. For the SEIR model, for example, the population is split into subgroups which are susceptible S, exposed E, infective I and recovered R. An example of a disease for which the SIR model is applicable is myxomatosis in rabbits [6]. Malaria has been modelled as a SIS disease [6], where a susceptible individual can become infectious and then susceptible again. More examples of compartment models can be found in [22, 30, 35, 37, 41].

For the standard SEIR model, recruitment of new individuals is into the susceptible class. Individuals in the infective class may or may not undergo disease

related death, depending on the disease. This model is applicable for diseases such as measles and varicella, which confer a permanent immunity, as once an individual has recovered, the individual does not re-enter the susceptible class. The transfer diagram follows.

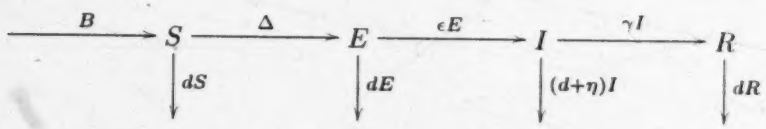

Figure 1.1: Transfer diagram for the SEIR model.

The number of new infections per unit time is the *incidence* Δ. Two commonly used forms of incidence in compartment models are mass action and proportional mixing (also called standard incidence). For mass action, it is assumed that the average number of contacts capable of transmitting the disease that an individual makes with infectious individuals per unit time, is proportional to the number of infectives. Multiplying by the number of susceptibles, we obtain, for the SEIR model, $\Delta = \beta SI$ where β is the contant of proportionality. In using proportional mixing, it is assumed that a typical individual makes a fixed number of contacts per unit time. The proportion of these contacts that are with infectives is equal to the proportion of infectives in the population. For the SEIR model we obtain $\Delta = \beta S\frac{I}{N}$ where $N = S + E + I + R$ is the total population. Other more general terms for the incidence may also be used. Different incidence terms are appropriate for different modeling situations.

For human diseases, standard incidence seems to more accurately conform to real-world data than does mass action incidence[2, 3]. This implies that within a given society, individuals have a similar number of daily contacts regardless of the size of the community in which they live.

The *force of infection* λ is the average number of disease transmitting contacts that a susceptible individual makes per unit time. Thus, if there is a single susceptible class of size S, then $\lambda S = \Delta$.

In the above transfer diagram, we have assumed that the rates at which individuals progress from E to I and from I to R are ϵE and γI, respectively. The recruitment B may be either a constant or a function of the state variables. The natural per capita death rate is d, and affects all groups equally. Individuals in the infective class have an additional per capita death rate of $\eta \geq 0$.

In [35], Li et al. resolve the existence of equilibria and their local stability for the SEIR model with $B = bN$ and proportional mixing incidence. Global stability is shown for $\eta < \epsilon$. In [37], Li and Muldowney demonstrate the existence and local stability of equilibria for $B = d$, $\eta = 0$ and incidence $\Delta = \beta S^q I^p$. Global stability is shown for $p \leq 1$.

1.3 The Reproduction Ratio

Let $Y = (X_1, \ldots, X_k)$ be the variables which represent population groups which are not infected with the disease, and let $Z = (X_{k+1}, \ldots, X_n)$ be the population groups which are infected. Each X_j, $j = 1, \ldots, n$ is assumed to be non-negative. For a well formulated model, if there is no disease in the population at time t_0 then there should be no disease in the population for $t > t_0$. Thus, if $Z(t) = 0$ then $Z'(t) = 0$.

Endemic equilibria are those for which $Z \neq 0$. Equilibria for which $Z = 0$ are referred to as *disease-free*. Many models exhibit a unique disease-free equilibrium. One of the principal questions that must be answered in the course of studying an epidemic model is whether or not a disease can "invade" a population in the

neighbourhood of an isolated disease-free equilibrium. In order to determine if this is possible, we consider the expected number R_0 of new infections caused by a typical infected individual in a completely susceptible population during the entire period of infectiousness. A more precise definition of R_0 can be found in [13]. In order for the disease to successfully invade a population, R_0 must be greater than one. In [13], Diekmann et al. make the following statement.

Threshold Criterion A. *The disease can invade if $R_0 > 1$, whereas it cannot if $R_0 < 1$.*

This assumes that there is no backward bifurcation at the disease-free equilibrium. In the presence of a backward bifurcation (see [57] for example), it is possible for the disease to persist in the population for some values of $R_0 < 1$ if there are a sufficient number of infectives.

The sign of $R_0 - 1$ is the same as the sign of the largest real part of an eigenvalue of the variational matrix at the disease-free equilibrium.

We now determine R_0 for the SEIR model studied in [37] for which there is a single disease-free equilibrium. A newly infected individual enters the exposed class, and is not yet infective. The probability that an exposed individual advances to the infective class (rather than dying) is $\frac{\epsilon}{\epsilon+d}$. Once an individual is in the infective class, the expected waiting time in that class is $\frac{1}{\gamma+d+\eta}$. Since the number of contacts that an individual makes per unit time is β, we find that $R_0 = \frac{\beta\epsilon}{(\gamma+d+\eta)(\epsilon+d)}$.

For some models, the population undergoes exponential growth or decay and so there are no equilibria. If the differential equation is homogeneous, then the proportion of the population in each group can be modelled. We are interested in the behaviour of $x_j = \frac{X_j}{N}$ for $j = 1, \ldots, n$ where $N = X_1 + \cdots + X_n$ is the total population size. The solutions of interest are those which lie in the simplex

$\Gamma = \{(x_1, \ldots, x_n) : x_1 + \cdots + x_n = 1\}$. In this case, disease-free equilibria correspond to points for which $z = \frac{Z}{N} = 0$ and $y = \frac{Y}{N}$ remain constant and endemic equilibria are those for which $z \neq 0$.

The threshold parameter for this system is called σ. Generally, σ is calculated by determining the local stability of the disease-free equilibrium. For the SEIR model studied in [35], $\sigma = \frac{\beta\epsilon}{(\gamma+b+\eta)(\epsilon+b)}$. An example of σ being calculated for a model of staged progression with amelioration can be found in Section 8.3. Generally, when analyzing a model in terms of the proportional variables, a result of the following form is demonstrated.

Threshold Criterion B. *The disease can invade in proportions if $\sigma > 1$, whereas it cannot if $\sigma < 1$.*

It is important to note that the sign of $R_0 - 1$ (or $\sigma - 1$) only determines the local stability of the disease-free equilibrium. The global behaviour must be determined separately. We also note that if $R_0 = 1$ (or $\sigma = 1$) then the stability is not immediately determined and further analysis is required.

1.4 Global Stability and Limit Sets

Consider the differential equation

$$x' = f(x) \tag{1.2}$$

where $x \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is C^1. Let $x(t; x_0)$ be the solution to (1.2) satisfying the initial condition $x(0) = x_0$. We say that y is an *omega limit point* of $x(t; x_0)$ if there is a sequence $\{t_n\}$ such that $\lim_{n\to\infty} t_n = \infty$ and $\lim_{n\to\infty} x(t_n; x_0) = y$. Let $\Omega(x_0)$ be the set of all omega limit points of the solution $x(t; x_0)$. Then by knowing $\Omega(x_0)$, we know the long-term behaviour of the solution through x_0. Often

it is possible to determine this long-term behaviour without being able to determine $x(t; x_0)$ exactly. Some easily shown properties of omega limit sets [20] follow.

Properties of Omega Limit Sets.

(A) $\Omega(x_0)$ *is invariant under (1.2).*

(B) If $\Omega(x_0)$ *consists of a single point* y*, then* y *is an equilibrium of (1.2).*

(C) If $\Omega(x_0)$ *consists of a simple closed curve containing no equilibria, then it is a periodic solution of (1.2).*

(D) $\Omega(x_0)$ *is closed.*

(E) If $\Omega(x_0)$ *is bounded, then it is non-empty and connected. If* $\Omega(x_0)$ *is not connected, then each connected component is unbounded.*

For a set D, let $\Omega(D) = \cup_{x_0 \in D} \Omega(x_0)$. If D is positively invariant and $\Omega(D)$ consists of a single point y, then y is an equilibrium and we say that y is *globally attracting in* D. If y is also locally asymptotically stable, then we say that y is *globally stable in* D. Similarly, if D is positively invariant and $\Omega(D)$ consists of a periodic orbit, we say the periodic orbit is globally attracting in D.

In the study of epidemics, an important consideration is the long-term behaviour of the system. It is desirable to determine whether the disease goes to a constant state (disease-free or endemic), whether there are periodic oscillations, or whether there is other stable behaviour. Suppose that equation (1.2) is a differential equation which models an infectious disease in a population and that D is the set for which all populations are non-negative and for which disease is present in the population. Then $\Omega(D)$ is of great interest. If $\Omega(D) = \{y\}$, then we know that if disease is present in the population then it will eventually go to the constant state given by y.

A point x_0 is called *wandering* if there exists $T \in \mathbb{R}$ and a neighbourhood N

of x_0 such that $x(t;N) \cap N$ is empty if $t > T$. Any omega limit point, for example, is non-wandering. Any condition which rules out the existence of non-constant non-wandering points will thus be useful in determining the structure of omega limit sets.

For planar systems, Bendixson's Criterion [7] for precluding the existence of periodic orbits is well known.

Bendixson's Criterion. *For $n = 2$, let D be a simply connected subset of $\mathbb{R}^2$ such that $div(f) \neq 0$ on D. Then there is no non-trivial periodic solution to equation (1.2) whose orbit lies entirely in D.*

For $n = 2$, if $\mathrm{div}(f) < 0$ then areas decrease under the flow described by (1.2). On the other hand, the area bounded by a non-trivial periodic orbit must remain constant, giving a contradiction. If $\mathrm{div}(f) > 0$, then by using a time reversal, the same argument applies. Although technically more complicated, a similar argument works in higher dimensions.

In [46], McCluskey and Muldowney show that if the assumptions of Bendixson's Criterion are met, then each bounded semi-trajectory limits to a single equilibrium.

By assigning weight functions to the plane, different measures of area can be found. By considering conditions which imply that these measures of area are strictly increasing or strictly decreasing, we obtain the following generalization [12] of Bendixson's Criterion.

Dulac's Criterion. *Let D be a simply connected subset of $\mathbb{R}^2$ and let $\alpha : D \to \mathbb{R}$ be C^1. For $n = 2$, if $div(\alpha f) \neq 0$ on D then there is no non-trivial periodic solution to equation (1.2) whose orbit lies entirely in D.*

Suppose C is a simple closed curve in $\mathbb{R}^n$ which is the trace of a periodic

solution of (1.2) for $n > 2$. Then there are an infinite number of surfaces which have C as their boundary. As each of these surfaces evolves according to the flow described by (1.2), the boundary of the new surfaces will still be C because under this flow, C is mapped onto itself.

There are three ways to consider the problem of ensuring the non-existence of periodic orbits. The direct analogs of the Bendixson and Dulac criteria pertain if, among all surfaces that have C as their boundary, there is one that minimizes the surface area. Under the map $x \to x(t; x_0)$, this minimal surface is mapped to other surfaces with boundary C. If surface areas decrease under the given dynamics, then for $t > 0$, this minimal surface is mapped onto surfaces with boundary C, but lesser area. This contradicts the minimality of the surface and so there can be no such curve C.

Secondly, suppose that among those surfaces which have the invariant curve C as their boundary, there is no surface that minimizes the surface area. There exists some $\delta > 0$ such that the surface area of any surface which has C as its boundary is greater than δ. If surface areas tend to zero under the flow, then C cannot be invariant.

Finally, using Stoke's Theorem it is possible to preclude the existence of invariant closed curves which are traversed with a particular orientation relative to a surface in which they lie.

The technical difficulties in n dimensions for $n > 2$ stem from the fact that the equation which describes the evolution of areas under the flow (1.2) involves the second additive compound of the Jacobian matrix. Since the Jacobian is a $n \times n$ matrix, the second additive compound has size $\binom{n}{2} \times \binom{n}{2}$. Compound matrices are discussed in Appendix A.

If a condition which implies surface areas decrease under the flow is C^1 ro-

bust, then by using Pugh's Closing Lemma [38, 51], it can be shown that all non-wandering points must be equilibria. Such conditions are called Bendixson Conditions. A more detailed discussion of Bendixson Conditions can be found in Chapter 3.

The ramifications of compound matrices for dynamics were first explored by Muldowney [47], who gave conditions which precluded the existence of periodic solutions to (1.2). This approach was further studied by Li and Muldowney [38, 39, 40] who studied the implications of such conditions for the global stability of dynamical systems as well as the development of similar conditions to be used in the presence of invariant manifolds. Li and others have found applications for these methods in epidemiological models [33, 35, 37, 41]. We present some of their results, as well as some new developments, in Chapter 3.

1.5 Thesis Summary

In Chapter 2, a strategy is presented for showing stability of linear systems. Traditionally, the stability of time-dependent linear systems has been shown by using the method of Lyapunov. If the Lyapunov function is a norm, then this is equivalent to finding a Lozinskii measure which is negative. In practice, the Lyapunov function is generally an absolute norm. The disadvantage of using an absolute norm is that it does not take into account the sign pattern of the derivative matrix. We present a strategy for developing non-absolute norms which are designed to take advantage of both the signs and the magnitudes of the entries in the derivative matrix.

Drawing on work by Li and Muldowney, Chapter 3 presents theorems which are used for showing the stability of differential equations. Theorems 3.11, 3.17,

3.18, and 3.19 are new material. In Section 3.3, theorems by Li and Muldowney are shown for demonstrating stability within an invariant manifold. The importance of this work is that it permits analysis of the system without the necessity of choosing a particular coordinate system within the manifold. In Section 3.4 this work is extended by characterizing all those dynamical systems whose restriction to the manifold is the same as the restriction of the system which is under consideration. Thus, the potential applicability of the work by Li and Muldowney is increased.

In Chapter 4, a test is given that can be used on a differential equation in three variables which is homogeneous of degree one in order to garner information about the limiting behaviour of orbits. The method is applied to a general example which includes SEIS and SIRS models.

In Chapter 5, several systems are studied which model the dynamics of an infectious disease and a gene that offers some protection from the disease. This work is motivated by the well known interaction between malaria and sickle cell anemia. The gene, which in homozygotes (those with two copies) causes sickle cell anemia, has the positive effect in heterozygotes (those with one copy) of increased immunity to malaria.

Chapter 6 presents a model of differential infectivity similar to that studied by Hyman et al. in [27]. The threshold parameter R_0 is calculated and the impact that it has on the presence and local stability of equilibria is determined. Using the techniques of Section 3.2, global stability is demonstrated for a subset of the parameter space.

In Chapter 7, a model of staged progression and amelioration is presented. The dynamics exhibited by the model are determined using the techniques developed in Section 3.4. In fact, it was through the analysis of the models in Chapters 7 and 8 that the observations upon which Section 3.4 is based, were first made.

Chapter 8 gives a more realistic, but algebraically more complicated, model of staged progression and amelioration. The resulting system of differential equations is homogeneous, so new equations are found to model the proportion of the population that is in each of the population groups. The threshold parameter σ is calculated and its implications for the disease-free equilibrium are demonstrated. Under restrictions on the parameters, the uniqueness and local stability of the endemic equilibrium are shown. Global stability is shown for a subset of the parameter space using the methods of Section 3.4.

In Chapter 9, the MSEIR model as presented by Hethcote in [22] is studied. In this model, the population is divided into the passively-immune class M, the susceptible class S, the exposed class E, the infective class I, and the recovered class R. In [22], the threshold parameter σ is calculated and it is shown that the disease-free equilibrium is globally stable for $\sigma < 1$. The global stability for $\sigma > 1$, however, is left unresolved. Some progress is made using the strategy described in Chapter 2. It is shown that the unique endemic equilibrium is globally stable for $\sigma > 1$ if the proportion of the population in class E at the endemic equilibrium is greater than the proportion in class M.

CHAPTER 2

Lozinskii Measures: A Strategy

2.1 Introduction

A *semi-norm* $\|\cdot\|$ on a linear space $\mathcal{L}$ is a real-valued function satisfying

(1) $\|x\| \geq 0$ for all $x \in \mathcal{L}$.

(2) $\|\alpha x\| = |\alpha| \, \|x\|$ for any scalar α and any $x \in \mathcal{L}$.

(3) $\|x + y\| \leq \|x\| + \|y\|$ for all $x, y \in \mathcal{L}$.

When $\|x\| = 0$ if and only if $x = 0$, then $\|\cdot\|$ is a *norm*. We note that norms and semi-norms are continuous functions.

Proposition 2.1. *Suppose that $B \subset \mathbb{R}^n$ is convex and that, if $0 \neq x \in R^n$, there exists $a \in (0, \infty)$ such that $tx \in B$ if and only if $|t| \leq a$. Then*

$$\|x\| = \begin{cases} 0 & \text{if } x = 0 \\ \frac{1}{a} & \text{if } x \neq 0 \end{cases}$$

defines a norm on $\mathbb{R}^n$.

We note that $x \in B$ if and only if $\|x\| \leq 1$. Specifically, we note that since B is convex, and contains points x and $-x$, for some x, we may conclude that $0 \in B$.

Proof of Proposition 2.1. It is easy to see that (1) and (2) are satisfied. To prove (3), we may assume that x and y are both non-zero. Let

$$\alpha = \frac{\|x\|}{\|x\| + \|y\|} \quad \text{and} \quad \beta = \frac{\|y\|}{\|x\| + \|y\|}.$$

Then $\alpha + \beta = 1$. Since $\frac{x}{\|x\|}, \frac{y}{\|y\|} \in B$ and B is convex,

$$\frac{x + y}{\|x\| + \|y\|} = \alpha \frac{x}{\|x\|} + \beta \frac{y}{\|y\|} \in B.$$

Thus,

$$\frac{\|x + y\|}{\|x\| + \|y\|} = \left\| \frac{x + y}{\|x\| + \|y\|} \right\| \leq 1,$$

which implies (3). □

Let $\|\cdot\|$ be a norm on $\mathbb{R}^n$. Associated with $\|\cdot\|$ is the induced matrix norm, which is also denoted by $\|\cdot\|$. For an $n \times n$ matrix M, we define

$$\|M\| = \sup_{\|x\|=1} \|Mx\|.$$

Also associated with $\|\cdot\|$ is a mapping $\mu : \mathbb{M}_{n\times n} \to \mathbb{R}$ called the *Lozinskii measure* [11]. This mapping is defined by

$$\mu(M) = \lim_{h\to 0^+} \frac{\|I + hM\| - 1}{h}.$$

Let $x = (x_1, \ldots, x_n)^T$ and $M = (b_{ij}) \in \mathbb{M}_{n\times n}$. Let ρ and λ be the largest eigenvalues of M^TM and $\frac{1}{2}(M^T + M)$ respectively. The following table can be found in [11].

Norm	$\|x\|$	$\|M\|$	$\mu(M)$
l_1	$\sum_{j=1}^n \|x_j\|$	$\max_i\left\{\sum_{j=1}^n \|b_{ij}\|\right\}$	$\max_j\left\{b_{jj} + \sum_{i\neq j} \|b_{ij}\|\right\}$
l_2	$\sqrt{\sum_{j=1}^n x_j^2}$	$\sqrt{\rho}$	λ
l_∞	$\max_j \|x_j\|$	$\max_j\left\{\sum_{i=1}^n \|b_{ij}\|\right\}$	$\max_i\left\{b_{ii} + \sum_{j\neq i} \|b_{ij}\|\right\}$

Table 2.1

Consider the linear system

$$x' = A(t)x \tag{2.1}$$

where $x \in \mathbb{R}^n$ and $A(t) \in \mathbb{M}_{n\times n}$. Let D_+ be the right-hand derivative [45]. Then

$$\begin{aligned} D_+\|x(t)\| &= \lim_{h\to 0^+} \frac{\|x(t+h)\| - \|x(t)\|}{h} \\ &= \lim_{h\to 0^+} \frac{\|x(t) + hA(t)x(t)\| - \|x(t)\|}{h} \\ &\leq \lim_{h\to 0^+} \frac{\|I + hA(t)\|\,\|x(t)\| - \|x(t)\|}{h} \\ &= \mu\big(A(t)\big)\,\|x(t)\| \end{aligned} \tag{2.2}$$

In fact,

$$\mu(B) = \inf\{c : D_+\|y\| \le c\|y\| \text{ for all solutions to } y' = By\}. \tag{2.3}$$

By (2.2), $\frac{1}{\|x(t)\|} D_+\|x(t)\| \le \mu(A(t))$. Integrating from 0 to T and rearranging, we see that $\|x(T)\| \le \|x(0)\| \exp\big(\int_0^T \mu(A(t))\,dt\big)$. Thus, if $\lim_{T\to\infty} \int_0^T \mu(A(t))\,dt = -\infty$, then each solution $x(t)$ to (2.1) goes to zero. A sufficient condition for the origin to be asymptotically stable is $\mu(A(t)) \le -\epsilon < 0$ for all t. Similarly,

$$-\mu(-B) = \sup\{c : D_+\|y\| \ge c\|y\| \text{ for all solutions to } y' = By\}$$

and so solutions of (2.1) also satisfy $\|x(T)\| \ge \|x(0)\| \exp\big(-\int_0^T \mu(-A(t))\,dt\big)$. If a matrix B has eigenvalues $\lambda_1, \ldots, \lambda_n$, then for any Lozinskii measure μ, we have $-\mu(-B) \le \mathrm{Re}(\lambda_j) \le \mu(B)$ for each j. A proof of this can be found in Coppel [11].

Proposition 2.2. *Let μ be a Lozinskii measure associated with the norm $\|\cdot\|$. Then $\mu(\alpha I + B) = \alpha + \mu(B)$ for any $\alpha \in \mathbb{R}$.*

Proof. Consider the system

$$y' = By. \tag{2.4}$$

For each solution $y(t)$ to (2.4) we define $z(t; y) = e^{\alpha t} y(t)$. Then $z' = (\alpha I + B)z$.

Suppose $D_+\|y(t)\| \le c\|y(t)\|$ for all solutions of (2.4). Then

$$\begin{aligned} D_+\|z(t)\| &= D_+\|e^{\alpha t} y(t)\| \\ &= \alpha e^{\alpha t}\|y(t)\| + e^{\alpha t} D_+\|y(t)\| \\ &\le \alpha e^{\alpha t}\|y(t)\| + c e^{\alpha t}\|y(t)\| \\ &= (\alpha + c)\|z(t)\|. \end{aligned}$$

Thus, by equation (2.3), we see that $\mu(\alpha I + B) \le \alpha + \mu(B)$. Similarly, by choosing c such that $D_+\|y(t)\| > c\|y(t)\|$ for some y and t, then it is easily shown that

$D_+\|z(t;y)\| > (\alpha+c)\|z(t;y)\|$. Thus, $\mu(\alpha I+B) \geq \alpha+\mu(B)$ and so the proposition is proven. □

For any particular norm $\|\cdot\|$ and matrix $A(t)$, the inequality (2.2) is the best possible in the sense that equality will always be achieved whenever $x(t)$ intersects a certain linear subspace of $\mathbb{R}^n$ of dimension at least 1. However, when $x(t)$ is in another location in the space, the growth rate bound given by (2.2) may be far from optimal for the particular equation (2.1) in question. As previously observed, different norms are associated with different measures and, for a given matrix $A(t)$, it is desirable to find a norm for which the associated Lozinskii measure is as low as possible. In this chapter we describe a constructive approach to discovering norms that give improved (i.e. lowered) growth estimates $\mu\big(A(t)\big)$ in (2.2) by taking advantage of the sign pattern of the matrix $A(t)$. For example, we will see for the particular 2-dimensional equation considered in the next section, that a 'hybrid norm' which coincides with the l_1 norm in the first and third quadrants and with the l_∞ norm in the second and fourth quadrants of the plane yields a Lozinskii measure that, for a given matrix, may be an improvement on those given by each of these norms.

2.2 A Two-Dimensional Motivational Example

Suppose

$$A(t) = \begin{bmatrix} a & b \\ -c & d \end{bmatrix}$$

where $b, c \geq 0$. If μ_p is the Lozinskii measure associated with the l_p norm then Table 2.1 gives

$$\mu_1(A) = \max\{a+c,\, d+b\}.$$

and

$$\mu_\infty(A) = \max\{a+b,\, d+c\}$$

Using equation (2.3), we now calculate μ for

$$\|x\| = \begin{cases} |x_1| + |x_2| & \text{if } \operatorname{sgn}(x_1) = \operatorname{sgn}(x_2) \\ \max\{|x_1|,\, |x_2|\} & \text{if } \operatorname{sgn}(x_1) = -\operatorname{sgn}(x_2). \end{cases}$$

Note that this defines $\|\cdot\|$ for the interior of each quadrant. On the axes, $\|\cdot\|$ is defined by continuity. Using Proposition 2.1, it is easily shown that $\|\cdot\|$ is a norm. To find an upper bound on the right-hand derivative of $\|x\|$, we do a case analysis.

Case 1. $\operatorname{sgn}(x_1) = \operatorname{sgn}(x_2)$

Then $\|x\| = |x_1| + |x_2| = |x_1 + x_2|$. Thus,

$$\begin{aligned} D_+\|x\| &= D_+|x_1 + x_2| \\ &= (a-c)\,|x_1| + (b+d)\,|x_2| \\ &\le \max\{a-c, b+d\}\,(|x_1| + |x_2|) \\ &= \max\{a-c, b+d\}\,\|x\|. \end{aligned} \tag{2.5}$$

Case 2. $\operatorname{sgn}(x_1) = -\operatorname{sgn}(x_2)$

Then $\|x\| = \max\{|x_1|,\, |x_2|\}$.

Case 2.A. $|x_1| > |x_2|$

Then

$$\begin{aligned} D_+\|x\| &= D_+|x_1| \\ &= a\,|x_1| - b\,|x_2| \\ &\le a\,\|x\|. \end{aligned} \tag{2.6}$$

Case 2.B. $|x_1| < |x_2|$

Then

$$\begin{aligned} D_+\|x\| &= D_+|x_2| \\ &= c\,|x_1| + d\,|x_2| \\ &\leq (c+d)\,|x_2| \\ &\leq (c+d)\,\|x\|. \end{aligned} \tag{2.7}$$

Equations (2.5), (2.6) and (2.7) imply $D_+\|x\| \leq \max\{a, b+d, c+d\}\|x\|$ almost everywhere. By continuity of the vector field, this relationship holds for all x. It should be noted that in the calculations which yield equations (2.5), (2.6) and (2.7), the inequalities that are used are optimal. Thus, (2.3) implies

$$\mu(A) = \max\{a, b+d, c+d\}. \tag{2.8}$$

Similarly, if

$$\|x\| = \begin{cases} \max\{|x_1|, |x_2|\} & \text{if } \operatorname{sgn}(x_1) = \operatorname{sgn}(x_2) \\ |x_1| + |x_2| & \text{if } \operatorname{sgn}(x_1) = -\operatorname{sgn}(x_2) \end{cases}$$

then

$$\mu(A) = \max\{a+b, a+c, d\}. \tag{2.9}$$

It is easy to see that there are situations for which one of equations (2.8) and (2.9) yields a Lozinskii measure which is less than each of μ_1 and μ_∞. Equations (2.8) and (2.9) are examples of Lozinskii measures that take advantage of the sign pattern of the matrix. For many epidemic models, the signs of the off-diagonal entries of the Jacobian matrix do not change. Thus, a similar approach may be very helpful in showing the stability of such systems.

2.3 Higher Dimensions

A *cone* $C \subseteq \mathbb{R}^n$ is a set which has the property that if $x \in C$ then $\alpha x \in C$ for all $\alpha \in \mathbb{R}_{\geq 0}$. For any semi-norm $\|\cdot\|$ on $\mathbb{R}^n$, the derivative $D_+\|x(t)\|$ does not in general satisfy an inequality of the form

$$D_+\|x(t)\| \leq \tau(t)\|x(t)\| \tag{2.10}$$

unless $x(t)$ is in some particular region of the space. For example, if $\|x\| = |x_1|$, where $x = (x_1, \ldots, x_n)^T$, then from

$$x_1' = a_{11}(t)x_1 + a_{12}(t)x_2 + \cdots + a_{1n}(t)x_n,$$

the best estimate on $D_+\|x(t)\|$ without some further restriction on $x(t)$ is

$$D_+\|x(t)\| \leq a_{11}|x_1(t)| + \sum_{j \neq 1} |a_{1j}(t)|\,|x_j(t)|, \tag{2.11}$$

so an inequality (2.10) is not satisfied in general. However, if $x(t)$ is in the cone C determined by

$$|x_j| \leq |x_1|,\ j \neq 1$$

then (2.11) implies that (2.10) is satisfied with

$$\tau(t) = a_{11}(t) + \sum_{j \neq 1} |a_{1j}(t)|.$$

This estimate on the growth rate may be further improved with different restrictions on C which take advantage of specific properties such as the signs of entries in $A(t)$. Suppose that $a_{12}(t) \leq 0$ for all t. Then in the cone C determined by

$$\operatorname{sgn}(x_1) = \operatorname{sgn}(x_2), \qquad |x_j| \leq |x_1|,\ j \neq 1, 2,$$

(2.10) is satisfied with $\tau(t) = a_{11}(t) + \sum_{j \neq 1,2} |a_{1j}(t)|$, an improvement on the previous growth estimate. If $a_{12}(t) \leq 0$ and $a_{13}(t) \geq 0$, then in the cone determined by

$$\text{sgn } (x_1) = \text{sgn } (x_2) = -\text{sgn } (x_3), \qquad |x_j| \leq |x_1|, \; j \neq 1, 2, 3,$$

(2.10) is satisfied with $\tau(t) = a_{11}(t) + \sum_{j \neq 1,2,3} |a_{1j}(t)|$.

In this thesis, we consider exclusively semi-norms $\| \cdot \|_i$ of the form

$$\|x\|_i = |x_{i_1}| + |x_{i_2}| + \cdots + |x_{i_k}|$$

and, by restrictions on the cone C_i, take advantage of the sign pattern exhibited by the matrix A to find improved values for τ_i. When this process leads to a subdivision of $\mathbb{R}^n$ into cones whose interiors are pairwise disjoint, we define

$$\|x\| = \|x\|_i \quad \text{for } x \in C_i.$$

If the resulting unit ball $\{x : \|x\| \leq 1\}$ has non-empty interior, is convex, and satisfies $\|x\| = 0$ if and only if $x = 0$, then $\| \cdot \|$ is a norm. Moreover, the corresponding Lozinskii measure satisfies

$$\mu\big(A(t)\big) \leq \tau(t) = \sup_i \tau_i(t).$$

The procedure described here may still be useful even if the resulting unit ball fails to be convex and $\| \cdot \|$ is not a norm. If the function $x \mapsto \|x\|$ is continuous and $0 < \|x\|$ if $x \neq 0$, then it may be used as a Lyapunov function and will still yield a bound on the rate of growth of solutions of (2.1).

We now present a strategy for constructing a norm for which the associated Lozinskii measure of a matrix $A(t)$ is below a given threshold $\tau(t)$. Clearly, this can only be done for appropriate τ.

Step 1. Consider semi-norms of the form

$$\|x\|_i = |x_{i_1}| + \cdots + |x_{i_k}| \tag{2.12}$$

where $1 \leq k \leq n$ and $1 \leq i_1 < \cdots < i_k \leq n$. For each orthant $\mathcal{O}$ determine which of these semi-norms satisfy

$$D_+\|x\|_i \leq \tau(t)\|x\|_i \tag{2.13}$$

under the dynamics described by (2.1) on either the entire orthant or on some cone contained in the orthant. We define a set $\mathcal{S}_\mathcal{O}$ of semi-norms on $\mathcal{O}$ as follows.

Let $\|x\|_* = \max_{j=1,\ldots,m}\{\|x\|_j\}$ where each $\|\cdot\|_j$ is of the form given in (2.12). Define the cone C_j for $j = 1, \ldots, m$ by $C_j = \{x \in \mathcal{O} : \|x\|_j \geq \|x\|_i \text{ for } i \neq j\}$. If (2.13) holds for $\|\cdot\|_j$ on C_j for $j = 1, \ldots, m$, then it also holds for $\|\cdot\|_*$ on $\mathcal{O}$. If (2.13) holds for $\|\cdot\|_*$ on $\mathcal{O}$ and $\|\cdot\|_*$ is non-zero when x is non-zero then $\|\cdot\|_* \in \mathcal{S}_\mathcal{O}$.

If $\mathcal{S}_\mathcal{O}$ is non-empty for each orthant $\mathcal{O}$ then we continue to Step 2.

Step 2. Determine if there is a norm $\|\cdot\|$ on $\mathbb{R}^n$ such that for each octant $\mathcal{O}$, the restriction of $\|\cdot\|$ to $\mathcal{O}$ is equivalent to $\|\cdot\|_*$ for some $\|\cdot\|_* \in \mathcal{S}_\mathcal{O}$. If so, then equation (2.13) is satisfied for $\|\cdot\|$ on $\mathbb{R}^n$ and therefore, by (2.3) the Lozinskii measure μ associated with $\|\cdot\|$ satisfies $\mu(A(t)) \leq \tau(t)$.

In practice, the linearity of equation (2.1) allows the orthants to be worked with in pairs $\mathcal{O}$ and $-\mathcal{O}$. We now present an example that is related to the MSEIR model of Chapter 9.

Example. Let

$$A(t) = \begin{bmatrix} -(\delta + b) & -b & 0 \\ \delta & -\beta(t) & 0 \\ 0 & \beta(t) & -(\epsilon + b) \end{bmatrix}$$

where δ, b, ϵ and $\beta(t)$ are all non-negative. We will construct a norm such that the corresponding Lozinskii measure is less than or equal to $\tau(t) = 0$.

Suppose $x_1, x_2, x_3 > 0$. Then $\|x\|_1 = |x_1|$, $\|x\|_2 = |x_1| + |x_2|$, and $\|x\|_3 = |x_1| + |x_2| + |x_3|$ each satisfy (2.13). In order that $\|x\|_*$ be non-zero for $x \neq 0$, $\|x\|_*$ must depend on each of x_1, x_2 and x_3. Since $\|x\|_1, \|x\|_2 < \|x\|_3$ the only choice for $\|\cdot\|_*$ is $\|\cdot\|_* = \|\cdot\|_3$. In order to facilitate referring to semi-norms in $\mathcal{S}_{\mathcal{O}}$ for different octants $\mathcal{O}$, we will label these semi-norms U_p for $p = 1, 2, \ldots$. Thus, we say $U_1 = \|\cdot\|_3$. By linearity, this choice also works for the negative octant $x_1, x_2, x_3 < 0$. We label this pair of octants $\mathcal{O}_{+++}$ and we have $\mathcal{S}_{\mathcal{O}_{+++}} = \{U_1\}$.

Let $\mathcal{O}_{++-}$ be the octants defined by sgn (x_1) = sgn (x_2) = $-$sgn (x_3). Then each of $\|x\|_4 = |x_1|$, $\|x\|_5 = |x_3|$, $\|x\|_6 = |x_1| + |x_2|$, $\|x\|_7 = |x_1| + |x_3|$ and $\|x\|_8 = |x_1| + |x_2| + |x_3|$ satisfies (2.13). To demonstrate how this is determined, we calculate an upper bound for $D_+\|x\|_7$ for the case when $x_1, x_2 > 0 > x_3$. We get

$$\begin{aligned}
D_+\|x\|_7 &= D_+(|x_1| + |x_3|) \\
&= D_+(x_1 - x_3) \\
&= x_1' - x_3' \\
&= -(\delta + b)x_1 - (b + \beta(t))x_2 + (\epsilon + b)x_3 \\
&\leq -(\delta + b)x_1 + (\epsilon + b)x_3 \\
&= -(\delta + b)|x_1| - (\epsilon + b)|x_3| \\
&\leq \max\{-(\delta + b), -(\epsilon + b)\}\ (|x_1| + |x_3|) \\
&= \max\{-(\delta + b), -(\epsilon + b)\}\ \|x\|_7.
\end{aligned}$$

Thus, $D_+\|x\|_7 \leq 0$. The other semi-norms are dealt with similarly. The choices for $\|\cdot\|_*$, such that (2.13) is satisfied and $\|x\|_* \neq 0$ for $x \neq 0$, are $U_2(x) = \|x\|_8$, $U_3(x) = \max\{\|x\|_5, \|x\|_6\} = \max\{|x_1|+|x_2|, |x_3|\}$, and $U_4(x) = \max\{\|x\|_6, \|x\|_7\} = \max\{|x_1| + |x_2|, |x_1| + |x_3|\}$. Thus, $\mathcal{S}_{\mathcal{O}_{++-}} = \{U_2, U_3, U_4\}$.

Let $\mathcal{O}_{+-+}$ be the pair of octants defined by sgn (x_1) = $-$sgn (x_2) = sgn (x_3).

Then (2.13) is satisfied by each of $\|x\|_9 = |x_1|$ on the cone $C_9 = \{x : |x_1| \geq |x_2|\}$, $\|x\|_{10} = |x_2|$, $\|x\|_{11} = |x_3|$, $\|x\|_{12} = |x_1| + |x_3|$ on $C_{12} = \{x : |x_1| + |x_3| \geq |x_2|\}$ and $\|x\|_{13} = |x_2| + |x_3|$. The choices for $\|\cdot\|_*$ which satisfy the necessary conditions are

$$U_5(x) = \max\{\|x\|_9, \|x\|_{10}, \|x\|_{11}\} = \max\{|x_1|, |x_2|, |x_3|\},$$

$$U_6(x) = \max\{\|x\|_9, \|x\|_{13}\} = \max\{|x_1|, |x_2| + |x_3|\},$$

$$U_7(x) = \max\{\|x\|_{10}, \|x\|_{12}\} = \max\{|x_1| + |x_3|, |x_2|\}$$

and $$U_8(x) = \max\{\|x\|_{12}, \|x\|_{13}\} = \max\{|x_1| + |x_3|, |x_2| + |x_3|\}.$$

Thus, $\mathcal{S}_{\mathcal{O}_{+-+}} = \{U_5, U_6, U_7, U_8\}$.

Finally, let $\mathcal{O}_{-++}$ be the octants defined by $-\text{sgn}\,(x_1) = \text{sgn}\,(x_2) = \text{sgn}\,(x_3)$. Then (2.13) is satisfied by $\|x\|_{14} = |x_1|$ on $C_{14} = \{x : |x_1| \geq |x_2|\}$, $\|x\|_{15} = |x_2|$ and $\|x\|_{16} = |x_2| + |x_3|$. The only satisfactory choice for $\|\cdot\|_*$ is $U_9(x) = \max\{\|x\|_{14}, \|x\|_{16}\} = \max\{|x_1|, |x_2| + |x_3|\}$. Thus $\mathcal{S}_{\mathcal{O}_{-++}} = \{U_9\}$.

We now determine whether or not there is a norm $\|\cdot\|$ on $\mathbb{R}^n$ such that for each octant $\mathcal{O}$, the restriction of $\|\cdot\|$ to $\mathcal{O}$ is equal to U_p for some $U_p \in \mathcal{S}_{\mathcal{O}}$. On $\mathcal{O}_{+++}$ and $\mathcal{O}_{-++}$ we must have $\|\cdot\| = U_1$ and $\|\cdot\| = U_9$, respectively. Note that the boundary between $\mathcal{O}_{+++}$ and $\mathcal{O}_{-++}$ is given by $x_1 = 0$. When $x_1 = 0$, $U_1 = U_9$, so there is no continuity problem.

Of the semi-norms in $\mathcal{S}_{\mathcal{O}_{++-}}$, only U_3 agrees with U_7 on the boundary between $\mathcal{O}_{-++}$ and $\mathcal{O}_{++-}$ which is given by $x_2 = 0$. U_3 also agrees with U_1 on the boundary between $\mathcal{O}_{+++}$ and $\mathcal{O}_{++-}$ given by $x_3 = 0$. Thus we must choose $\|\cdot\| = U_3$ on $\mathcal{O}_{++-}$.

Of the semi-norms in $\mathcal{S}_{\mathcal{O}_{+-+}}$, only U_7 continuously extends $\|\cdot\|$ into $\mathcal{O}_{+-+}$.

Thus, we may now write

$$\|x\| = \begin{cases} |x_1| + |x_2| + |x_3| & \text{if } \operatorname{sgn}(x_1) = \operatorname{sgn}(x_2) = \operatorname{sgn}(x_3) \\ \max\{|x_1| + |x_2|, |x_3|\} & \text{if } \operatorname{sgn}(x_1) = \operatorname{sgn}(x_2) = -\operatorname{sgn}(x_3) \\ \max\{|x_1| + |x_3|, |x_2|\} & \text{if } \operatorname{sgn}(x_1) = -\operatorname{sgn}(x_2) = \operatorname{sgn}(x_3) \\ \max\{|x_1|, |x_2| + |x_3|\} & \text{if } -\operatorname{sgn}(x_1) = \operatorname{sgn}(x_2) = \operatorname{sgn}(x_3) \end{cases}$$

Let μ be the Lozinskii measure associated with $\|\cdot\|$. Then by (2.3), $\mu(A(t)) \leq 0$ for all t. In fact, it can be shown that $\mu(A(t))$ is exactly zero.

CHAPTER 3

Stability Theorems

3.1 Surface Functionals

In this chapter, we explore conditions which imply that two-dimensional areas in R^n decrease as they evolve under the dynamics described by an ordinary differential equation. It will be shown that such conditions have strong implications for global stability.

Let B be the Euclidean ball in $\mathbb{R}^2$ and let $\bar{B}$ and ∂B be its closure and boundary, respectively. If $H \subset \mathbb{R}^n$ is open, then a function $\varphi \in \text{Lip}(\bar{B} \to H)$ will be described as a simply connected rectifiable 2-surface in H or, more briefly, as a surface. A function $\psi \in \text{Lip}(\partial B \to H)$ is a closed rectifiable curve in H and will be called simple if it is one-to-one. Let $\Sigma(\psi, H) = \{\varphi \in \text{Lip}(\bar{B} \to H) : \varphi|_{\partial B} = \psi\}$. In [42], Li and Muldowney show that if H is simply connected, then $\Sigma(\psi, H)$ is non-empty for each simple closed rectifiable curve ψ in H.

Let $\|\cdot\|$ be a norm on $\mathbb{R}^{\binom{n}{2}}$. Consider a functional $\mathcal{S}$ on surfaces in H defined by

$$\mathcal{S}\varphi = \int_{\bar{B}} \left\| \frac{\partial \varphi}{\partial u_1} \wedge \frac{\partial \varphi}{\partial u_2} \right\| \tag{3.1}$$

where $u = (u_1, u_2)$ and $u \mapsto \varphi(u)$ is Lipschitzian on $\bar{B}$. The following result is shown in [42].

Proposition 3.1. *Suppose ψ is a simple closed rectifiable curve in $\mathbb{R}^n$. Then there exists $\delta > 0$ such that*

$$\mathcal{S}\varphi \geq \delta$$

for all $\varphi \in \Sigma(\psi, \mathbb{R}^n)$.

3.2 Stability Theorems

Consider the differential equation

$$x' = f(x) \tag{3.2}$$

where $x \in H \subseteq \mathbb{R}^n$ and $f : H \to \mathbb{R}^n$ is C^1. For a surface φ, we define the surface φ_t by $\varphi_t(u) = x\big(t; \varphi(u)\big)$. Note that, when viewed as a function of t, $\varphi_t(u)$ gives the solution to (3.2) which passes through the point $\varphi(u)$ at $t = 0$.

It is shown in [42] that for a surface φ and a functional $\mathcal{S}$ given by (3.1) that $D_+\mathcal{S}\varphi_t$, the right-hand derivative [45] of $\mathcal{S}\varphi_t$ with respect to time, is given by

$$D_+\mathcal{S}\varphi_t = \int_{\bar{B}} \lim_{h \to 0^+} \Big[\big|\big| z + h \frac{\partial f}{\partial x}^{[2]} \big(\varphi_t(u)\big) z \big|\big| - ||z|| \Big] \tag{3.3}$$

where $z = \frac{\partial \varphi_t}{\partial u_1} \wedge \frac{\partial \varphi_t}{\partial u_2}$. As seen in Appendix A, $z(t)$ is a solution of

$$z' = \frac{\partial f}{\partial x}^{[2]} \big(\varphi_t(u)\big) z \tag{3.4}$$

and so equation (3.3) can be rewritten as

$$D_+\mathcal{S}\varphi_t = \int_{\bar{B}} D_+ \|z\|. \tag{3.5}$$

We are interested in the implications that the stability of (3.4) has for the limiting behaviour of solutions of (3.2). Let μ be the Lozinskii measure associated with the norm $\|\cdot\|$. Then by equation (2.3),

$$\begin{aligned} D_+\mathcal{S}\varphi_t &\leq \int_{\bar{B}} \Big[\mu\Big(\frac{\partial f}{\partial x}^{[2]} \big(\varphi_t(u)\big) \Big) \|z\| \Big] \\ &\leq \Big[\sup_{u \in \bar{B}} \mu\Big(\frac{\partial f}{\partial x}^{[2]} \big(\varphi_t(u)\big) \Big) \Big] \int_{\bar{B}} \|z\| \\ &= \Big[\sup_{u \in \bar{B}} \mu\Big(\frac{\partial f}{\partial x}^{[2]} \big(\varphi_t(u)\big) \Big) \Big] \mathcal{S}\varphi_t. \end{aligned} \tag{3.6}$$

Suppose that φ maps $\bar{B}$ into a set K which is positively invariant and that $\sup_{x\in K}\mu\Big(\frac{\partial f}{\partial x}^{[2]}(x)\Big) = \alpha$. Then

$$D_+\mathcal{S}\varphi_t \le \alpha\,\mathcal{S}\varphi_t$$

for all t and therefore $\mathcal{S}\varphi_t \le e^{\alpha t}\mathcal{S}\varphi$. If $\alpha > 0$ then this gives a bound on how quickly surface areas in K can grow in area. If $\alpha < 0$ then this gives a bound on how quickly surface areas must shrink in K.

A compact set K is called *absorbing* if each compact set $H_1 \subset H$ satisfies $x(t; H_1) \subset K$ for sufficiently large t.

We consider the following hypotheses.

(H1) H is simply connected.

(H2) There is a compact absorbing set $K \subset H$.

(H3) Under (3.2), there is a unique equilibrium $\bar{x} \in H$.

Note that if (H2) and (H3) both hold, then $\bar{x}$ necessarily lies in the set K. We now present criteria for ruling out periodic solutions of equation (3.2).

Proposition 3.2. *If (H1) and (H2) are satisfied and*

$$\sup_{x\in K}\mu\Big(\frac{\partial f}{\partial x}^{[2]}(x)\Big) < 0 \tag{3.7}$$

then there are no non-constant periodic solutions to (3.2).

Proof. Let ψ be the trace of a periodic solution to (3.2) and let $\varphi \in \Sigma(\psi, H)$. Since K is absorbing, ψ must lie in the set K and we may assume that φ is also in K. Let $\alpha = \sup_{x\in K}\mu\Big(\frac{\partial f}{\partial x}^{[2]}(x)\Big)$. Equations (3.6) and (3.7) imply $D_+\mathcal{S}\varphi_t \le \alpha\mathcal{S}\varphi_t$ and therefore $\mathcal{S}\varphi_t \le e^{\alpha t}\mathcal{S}\varphi$. Since $\alpha < 0$, we see that $\lim_{t\to\infty}\mathcal{S}\varphi_t = 0$.

On the other hand, $\varphi_t(\partial B) = x\big(t;\varphi(\partial B)\big) = x\big(t;\psi\big) = \psi$ and so φ_t is a surface whose boundary is ψ. But by Proposition 3.1, $\mathcal{S}\varphi_t \ge \delta > 0$ for all t, giving a contradiction. □

It is clear that (3.7) is a strong restriction. An examination of the previous proof, however, shows that any condition that guarantees $\lim_{t\to\infty} \frac{\partial\varphi_t}{\partial u_1} \wedge \frac{\partial\varphi_t}{\partial u_2} = 0$, uniformly with respect to $u \in B$ implies that $\lim_{t\to\infty} \mathcal{S}\varphi_t = 0$, thus precluding the existence of non-constant periodic solutions. Thus, for example, if

$$\limsup_{T\to\infty} \sup_{x_0\in K} \frac{1}{T}\int_0^T \mu\Big(\frac{\partial f}{\partial x}^{[2]}\big(x(t;x_0)\big)\Big)dt < 0$$

then the asymptotic restriction on areas originating in K required for the conclusion of Proposition 3.2 is still satisfied.

More generally, if instead of surface functionals of the form given in equation (3.1), we consider

$$\mathcal{S}\varphi = \int_B \Big\| Q(\varphi)\,\frac{\partial\varphi}{\partial u_1} \wedge \frac{\partial\varphi}{\partial u_2}\Big\|$$

where $x \mapsto Q(x)$ is a C^1 non-singular $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function. The time-evolution of $\mathcal{S}\varphi_t$ may now be analyzed as before by considering the change of variable $w = Qz$ so that (3.4) is transformed to

$$w' = \Big[Q_f Q^{-1} + Q\frac{\partial f}{\partial x}^{[2]} Q^{-1}\Big]_{x(t;x_0)} w \tag{3.8}$$

where Q_f is the directional derivative of Q in the direction of the vector field f. This can be thought of as replacing each entry of Q with its time derivative. As long as the dynamics are restricted to a region where $|Q^{-1}|$ is bounded, as is the situation when there is a compact absorbing set, then the conclusion of Proposition 3.1, $\mathcal{S}\varphi \geq \delta$, still holds and the analysis may be conducted as before, if $\mathcal{S}\varphi_t \to 0$ as $t \to \infty$.

Following the work of Li and Muldowney in [38], for a compact set K and a Lozinskii measure μ, we define

$$\bar{q}_2 = \limsup_{T\to\infty} \sup_{x_0\in K} \frac{1}{T}\int_0^T \mu\Big[Q_f Q^{-1} + Q\frac{\partial f}{\partial x}^{[2]} Q^{-1}\Big]_{x(t;x_0)} dt. \tag{3.9}$$

Then, as in Proposition 3.2, we have the following conclusion.

Proposition 3.3. *If (H1) and (H2) are satisfied and*

$$\bar{q}_2 < 0, \tag{3.10}$$

then there are no non-constant periodic solutions to (3.2).

Following Li and Muldowney in [36], we now use a result by Pugh [50, 51] to extend this result, ruling out other non-constant non-wandering points.

Lemma 3.4 - Pugh's C^1 Closing Lemma. *If x_0 is a non-equilibrium non-wandering point with respect to the flow of a C^1 vector field f and the orbit of x_0 has compact closure, then every neighbourhood of f in the space of C^1 vector fields contains a vector field $\hat{f}$ having a periodic orbit through x_0. Moreover, $\hat{f}$ can be chosen to agree with f outside of a given neighbourhood of x_0.*

It is shown in [38] that (3.10) is robust under local C^1 perturbations. Thus, we see that if f meets the assumptions of Proposition 3.2, then so must all nearby vector fields. Thus f can have no non-constant non-wandering points. The following result is proven by Li and Muldowney in [38].

Theorem 3.5. *If (H1) and (H2) are satisfied and $\bar{q}_2 < 0$ then no simple closed rectifiable curve in H can be invariant with respect to (3.2). Further, there are no non-constant non-wandering points and every non-empty alpha or omega limit set is a single equilibrium.*

Note that when applicable, Theorem 3.5 precludes the existence of periodic orbits, homoclinic orbits and heteroclinic cycles. We now include hypothesis (H3) to obtain the following result found in [38].

Theorem 3.6. *If (H1), (H2) and (H3) are satisfied and $\bar{q}_2 < 0$ then the unique equilibrium $\bar{x}$ is globally asymptotically stable in H.*

We now consider the implications of equation (3.8) being stable for a particular solution $x(t;x_0)$ of (3.2) which is bounded. In the following theorems, the definitions of uniformly asymptotically stable and orbitally asymptotically stable agree with the standard definitions found in [11] and [20], for example. The following result is proven by Li and Muldowney in [39].

Theorem 3.7. *Let $x(t;x_0)$ be a bounded solution of (3.2) with omega limit set Ω. If (3.8) is uniformly asymptotically stable then Ω either contains an equilibrium or is a periodic orbit.*

Corollary 3.8. *Let $x(t;x_0)$ be a bounded solution of (3.2) with omega limit set Ω. If*

$$\limsup_{T\to\infty} \frac{1}{T}\int_0^T \mu\Big(\Big[Q_f Q^{-1} + Q\,\frac{\partial f}{\partial x}^{[2]} Q^{-1}\Big]_{x(t;x_0)}\Big)\,dt < 0$$

then Ω either contains an equilibrium or is a periodic orbit.

Next, we look at the case where $x(t;x_0)$ is a non-trivial periodic solution of (3.2) and equation (3.8) is asymptotically stable. In [47], Muldowney proves the following result.

Theorem 3.9. *Let $x(t;x_0)$ be a periodic solution of (3.2) with least period $\omega > 0$. A sufficient condition for x to be orbitally asymptotically stable is that equation (3.8) is asymptotically stable.*

Corollary 3.10. *Let $x(t;x_0)$ be a periodic solution of (3.2) with least period $\omega > 0$. If*

$$\int_0^\omega \mu\Big(\Big[Q_f Q^{-1} + Q\,\frac{\partial f}{\partial x}^{[2]} Q^{-1}\Big]_{x(t;x_0)}\Big)\,dt < 0 \tag{3.11}$$

then x is orbitally asymptotically stable.

We now present a new theorem which can be used to show that an equilibrium on the boundary of a compact set is globally stable. This theorem will be useful in

the study of epidemic models where the compact set is often the set for which the size of each population group is non-negative and the total population is below a given bound.

Theorem 3.11. *Let D be a compact, simply connected set with boundary ∂D. Suppose D is positively invariant under (3.2) and that the only equilibrium in D is $P \in \partial D$. Further, suppose that P is locally asymptotically stable and is the only omega limit point in ∂D. If*

$$\limsup_{T\to\infty} \frac{1}{T}\int_0^T \mu\Big(\Big[Q_f Q^{-1} + Q\frac{\partial f}{\partial x}^{[2]} Q^{-1}\Big]_{x(t;x_0)}\Big)\, dt < 0 \tag{3.12}$$

for each solution which is bounded away from ∂D then all solutions limit to P.

Proof. Let U be the basin of attraction of P in D. If $U = D$ then the result follows. Suppose that U is a proper subset of D. Let $x(t;x_0)$ be a solution to (3.2) that lies in the boundary of U and let Ω be its omega limit set. Then Ω also lies in the boundary of U. Since P is the only omega limit point in ∂D and x does not lie in its basin of attraction, Ω must be bounded away from ∂D and therefore, trajectories in Ω must satisfy (3.12).

Since $P \notin \Omega$ is the only equilibrium in D, Corollary 3.8 implies that Ω is a periodic orbit. For an ω-periodic orbit, (3.11) and (3.12) are equivalent, so by Corollary 3.10, Ω is orbitally asymptotically stable. But, this contradicts the fact that Ω lies in the boundary of U. Thus there can be no such solution x and so $U = D$. □

3.3 Stability Theorems for Systems with Invariant Manifolds

Let $x \mapsto V(x)$ be a $\mathbb{R}^m$-valued C^2 function and let Γ denote the subset of $\mathbb{R}^n$ where $V(x) = 0$. Then Γ is a manifold of dimension $n - m$ if $\operatorname{rank}(\frac{\partial V}{\partial x}) = m$

when $V(x) = 0$ and Γ is invariant with respect to (3.2) if $V(x_0) = 0$ implies that $V(x(t; x_0)) = 0$ for all t. We say that Γ has codimension m. In [40], Li and Muldowney prove the following.

Proposition 3.12. *Let Γ be a $(n - m)$ dimensional manifold given by $V(x) = 0$. Then Γ is invariant if and only if there is a continuous $m \times m$ matrix-valued function $N_{(f)}(x)$ such that*

$$V_f(x) = N_{(f)}(x)V(x). \tag{3.13}$$

Remark. For clarity, we emphasize that V_f refers to the directional derivative of V in the direction of the vector field f, while the subscript in $N_{(f)}$ merely labels N as having dependence on f.

Definition. *For an invariant manifold Γ, let $\nu_{(f)}$ be the real-valued function defined on Γ by*

$$\nu_{(f)}(x) = tr\, N_{(f)}(x) \tag{3.14}$$

where $N_{(f)}(x)$ is defined by (3.13).

Although, $N_{(f)}(x)$ may not be uniquely defined for all of $\mathbb{R}^n$ when $m > 1$, $N_{(f)}$ is uniquely defined on Γ [40]. Thus, $\nu_{(f)}$ is also uniquely defined on Γ.

In order to rule out periodic orbits in an invariant manifold, it is necessary to find a condition which implies that some measure of two-dimensional areas in the manifold decreases under the dynamics described by (3.2). Let Γ be an invariant manifold of codimension m. It is shown in [40] that if

$$z' = \left[\frac{\partial f}{\partial x}^{[m+2]} - \nu_{(f)}I\right]_{x(t;x_0)} z \tag{3.15}$$

is uniformly asymptotically stable for a solution $x(t; x_0)$ in Γ, then in the long-term, infinitesimal two-dimensional areas in Γ decrease as they flow along the trajectory of x.

Remark. To aid intuition, we note that it is shown in [40] that $\nu_{(f)}(x)$ describes the rate of growth of m-dimensional volumes which are the exterior product of vectors which are normal to Γ at x. The matrix $\frac{\partial f}{\partial x}^{[m+2]}$ governs the growth of $(m+2)$-dimensional volumes, including volumes which are the exterior product of m vectors that are normal to Γ and two vectors which are tangent to Γ. It is this class of volumes that is of interest. By decoupling these volumes into normal and tangent components, it can be shown that the rate of growth of areas in Γ is governed by (3.15).

Let Q be a C^1 nonsingular $\binom{n}{m+2} \times \binom{n}{m+2}$ matrix-valued function such that $|Q^{-1}|$ is bounded and let $w = Qz$. Then

$$w' = M_{(f)}w \tag{3.16}$$

where

$$M_{(f)}(x(t;x_0)) = \left[Q_f Q^{-1} + Q\frac{\partial f}{\partial x}^{[m+2]} Q^{-1} - \nu_{(f)}I\right]_{x(t;x_0)}. \tag{3.17}$$

When there is no risk of confusion the subscripts in $M_{(f)}$, $N_{(f)}$ and $\nu_{(f)}$ will be omitted.

The stability of equation (3.16) is the same as the stability of (3.15). Thus, if equation (3.16) is uniformly asymptotically stable, then in the long-term, infinitesimal two-dimensional areas in Γ decrease as they flow along $x(t;x_0)$, a solution to (3.2).

By considering Lyapunov functions of the form $\|w\|$, we see that for a particular solution x of (3.2), equation (3.16) is uniformly asymptotically stable if

$$\lim_{T\to\infty} \int_0^T \mu\Big(M\big(x(t;x_0)\big)\Big)dt = -\infty$$

where μ is the Lozinskii measure corresponding to $\|\cdot\|$.

For a compact set $K \subseteq \Gamma$, let

$$\bar{q}_{m+2} = \limsup_{T\to\infty} \sup_{x_0\in K} \frac{1}{T}\int_0^T \mu\Big(M\big(x(t,x_0)\big)\Big)\,dt. \tag{3.18}$$

We note that although $\bar{q}_{m+2}$ is a function of f and Q this is suppressed in the notation. Geometrically, $\bar{q}_{m+2}$ can be thought of as the long-term average of the maximum rate of growth of two-dimensional areas starting in $K \subseteq \Gamma$.

Consider the following hypotheses.

(H4) Γ is simply connected.

(H5) There is a compact set $K \subseteq \Gamma$ which is absorbing in Γ.

(H6) There is a unique equilibrium $\bar{x} \in \Gamma$.

The following two theorems are proven by Li and Muldowney in [40].

Theorem 3.13. *If (H4) and (H5) are satisfied and $\bar{q}_{m+2} < 0$ then no simple closed rectifiable curve in Γ can be invariant with respect to (3.2). Further, there are no non-constant non-wandering points and every alpha or omega limit set consists of a single equilibrium.*

Theorem 3.14. *If (H4), (H5) and (H6) are satisfied and $\bar{q}_{m+2} < 0$ then the unique equilibrium $\bar{x}$ is globally asymptotically stable in Γ.*

Next, we consider the case where equation (3.15) is stable for a non-trivial periodic solution of (3.2) which lies in the invariant manifold Γ. The following result can be found in [40].

Theorem 3.15. *Let $x(t;x_0)$ be a periodic solution of (3.2) in Γ with least period $\omega > 0$. A sufficient condition for x to be orbitally asymptotically stable is that equation (3.15) is asymptotically stable.*

Corollary 3.16. *Let $x(t;x_0)$ be a periodic solution of (3.2) in Γ with least period $\omega > 0$. If*

$$\int_0^\omega \mu\Big(M\big(x(t;x_0)\big)\Big)\,dt < 0$$

then x is orbitally asymptotically stable.

Remark. Although an analogue to Theorem 3.7 in the presence of invariant manifolds is almost surely true, it has not yet been proven. Thus, care must be taken in providing an analogue to Theorem 3.11.

We now present a version of Pugh's C^1 Closing Lemma which is valid on invariant manifolds. A point $x_0 \in \Gamma$ is *wandering* with respect to the flow on Γ if there exists a neighbourhood N in Γ of x_0 and $t_1 > 0$ such that $x(t;N) \cap N$ is empty if $t \geq t_1$. Pugh's C^1 Closing Lemma [50, 51] states that if x_0 is a non-constant non-wandering point with respect to the flow on Γ and the orbit through x_0 has compact closure, then every neighbourhood of f in the space of C^1 vector fields on Γ contains a vector field $\hat{f}$ having a periodic orbit through x_0. Moreover, $\hat{f}$ can be chosen to agree with f outside a given neighbourhood N of x_0.

Theorem 3.17. *Let $D \subseteq \Gamma$ be a compact, simply connected set with boundary ∂D. Suppose D is positively invariant under (3.2) and that the only equilibrium in D is $P \in \partial D$. Further, suppose that P is locally asymptotically stable in Γ and is the only omega limit point in ∂D. If*

$$\mu(M_{(f)}) < 0 \tag{3.19}$$

on D, then all solutions beginning in D limit to P.

Proof. Let U be the basin of attraction of P in D. If $U = D$ then the result follows. Suppose U is a proper subset of D. Then there are omega limit points in

the interior of D which are not in U. Let x_0 be such a point. Clearly, $x_0 \neq P$, so x_0 is a non-equilibrium non-wandering point.

Let $\|\cdot\|_2$ denote the standard Euclidean norm and the matrix norm that it induces. Fix $\epsilon > 0$ such that $\|f(x_0)\|_2 > 2\epsilon$. Choose $\delta > 0$ such that $\|f(x) - f(x_0)\|_2 < \epsilon$ and $\|\frac{\partial f}{\partial x}(x) - \frac{\partial f}{\partial x}(x_0)\|_2 < \epsilon$ for all x in $B_\delta = \{x \in \mathbb{R}^n : \|x - x_0\|_2 < \delta\}$ and such that $\tilde{B}_\delta = B_\delta \cap D$ is connected. We assume that $\tilde{B}_\delta$ is bounded away from the boundary of D.

By Pugh's Closing Lemma, there is a C^1 vector field h on Γ such that

$$x' = h(x) \tag{3.20}$$

leaves Γ invariant, supp $(h - f) \subset \tilde{B}_\delta$, $\|h - f|_\Gamma\|_{C^1} < \epsilon$, and there is a periodic solution to (3.20) through x_0 with trace ψ.

Let $T \subset H$ be a tubular neighbourhood of D. Then for each $x \in T$ there is a unique $y \in \Gamma$ and v normal to Γ at y such that $x = y + v$. Furthermore, $y(x)$ and $v(x)$ are C^1 functions of x. See the Tubular Neighbourhood Theorem, in [24] for example. Since D is compact, we can assume that $\frac{\partial y}{\partial x}$ is bounded on T by say $k_1 > 0$.

We now show that h can be extended to a vector field g on T which is C^1 close to f. Let g be defined by

$$g(x) = f(x) + h\big(y(x)\big) - f\big(y(x)\big)$$

for all $x \in T$. Then

$$x' = g(x) \tag{3.21}$$

leaves Γ invariant and there is a periodic solution to (3.21) through x_0. We note

that $\|g(x) - f(x)\| = \|h(y) - f(y)\|$ and

$$\begin{aligned}\left\|\frac{\partial g}{\partial x} - \frac{\partial f}{\partial x}\right\| &= \left\|\frac{\partial}{\partial x}\big(h(y) - f(y)\big)\right\| \\ &= \left\|\frac{\partial}{\partial y}\big(h(y) - f(y)\big)\,\frac{\partial y}{\partial x}\right\| \\ &\le k_1 \left\|\frac{\partial}{\partial y}\big(h(y) - f(y)\big)\right\|.\end{aligned}$$

Thus, since $\|h - f\|_{C^1} < \epsilon$ on Γ, $\|g - f\|_{C^1} < (1 + k_1)\epsilon$ on T. We note that in $D \setminus B_\delta$, $g = f$ and $\frac{\partial g}{\partial x} = \frac{\partial f}{\partial x}$.

Suppose $Q = [q_{ij}]$ where $\|\nabla q_{ij}\| < k_2$ on D for $i, j = 1, \ldots, n$. Then $Q_g = [\nabla q_{ij} \cdot g]$. Expressing Q_f similarly, we see that $Q_g - Q_f = [\nabla q_{ij} \cdot (g - f)]$. Thus, each entry of $Q_g - Q_f$ is bounded in absolute value by $k_2\epsilon\binom{n}{m+2}$.

It is shown in [40] that on Γ, $N_{(g)}$ is determined by the relationship

$$\frac{\partial}{\partial x}\Big(\frac{\partial V}{\partial x} \cdot g\Big) = N_{(g)}\frac{\partial V}{\partial x}.$$

Since $N_{(f)}$ satisfies a similar relationship, we see that

$$\frac{\partial}{\partial x}\Big(\frac{\partial V}{\partial x} \cdot (g - f)\Big) = \big(N_{(g)} - N_{(f)}\big)\frac{\partial V}{\partial x}. \tag{3.22}$$

Since V is C^2 on D which is compact, g is C^1 close to f, and $\frac{\partial V}{\partial x}$ has full rank on Γ, equation (3.22) implies that on Γ, each entry of $N_{(g)} - N_{(f)}$ is bounded in absolute value by $k_3\epsilon$ on D for some k_3 which is independent of ϵ. Thus, $|\nu_{(g)} - \nu_{(f)}| < mk_3\epsilon$.

Applying equation (3.17) to both g and f and subtracting gives

$$M_{(g)} - M_{(f)} = (Q_g - Q_f)Q^{-1} + Q\Big[\frac{\partial}{\partial x}(g - f)\Big]^{[m+2]}Q^{-1} - \big(\nu_{(g)} - \nu_{(f)}\big)I$$

Thus, there exists $k_4 > 0$ which is independent of ϵ such that each entry of $M_{(g)} - M_{(f)}$ is bounded in absolute value by $k_4\epsilon$. Since the Lozinskii measure

of a matrix depends continuously on the elements of the matrix, we see that if $-\alpha = \sup_D \mu\big(M_{(f)}\big) < 0$ then by choosing ϵ and δ sufficiently small, we obtain

$$\mu\big(M_{(g)}\big) \leq -\frac{\alpha}{2}$$

on D.

Since the set D is positively invariant under (3.2), it is also positively invariant under (3.21). Let $\varphi \in \Sigma(\psi, D)$. Then under the flow described by (3.21), $\varphi_t \in \Sigma(\psi, D)$ for all t. Therefore $\mathcal{S}\varphi_t \leq \mathrm{e}^{-\frac{\alpha}{2}t}\mathcal{S}\varphi$ and so, $\lim_{t\to\infty} \mathcal{S}\varphi_t = 0$. This contradicts Proposition 3.1. Therefore, the assumption that $U \neq D$ must be incorrect. □

3.4 Equivalent Embeddings of the Dynamics on an Invariant Manifold

Many of the advances of this thesis are facilitated through the observation that a dynamical system which has an invariant manifold is only one of an infinite class of systems that exhibit the same behaviour on the manifold. If a solution can be shown to be stable relative to the dynamics within the invariant manifold for any single system in this class, then the same result will necessarily be true for the entire class.

We now assume that (3.2) has an invariant manifold Γ of codimension m which is given by $V(x) = 0$ and suppose that we are only interested in the dynamics within Γ. Then we may replace (3.2) with

$$x' = F(x) \tag{3.23}$$

where

$$F(x) = f(x) + E(x)V(x) \tag{3.24}$$

and $E(x)$ is any continuous $n \times m$ matrix-valued function defined in a neighbourhood of Γ. When restricted to Γ, the dynamics described by (3.23) are the same as those described by (3.2). The associated Jacobians, however, may differ and since it is often the Jacobians that are used in stability analysis, this can be a useful tool.

We now reformulate equations (3.13) and (3.14) in this context.

$$\begin{aligned} N_{(F)}V &= V_F \\ &= \frac{\partial V}{\partial x} \cdot F \\ &= \frac{\partial V}{\partial x} \cdot (f + EV) \\ &= N_{(f)}V + \frac{\partial V}{\partial x} EV \end{aligned}$$

By choosing $N_{(F)} = N_{(f)} + \frac{\partial V}{\partial x} E$ and using (3.14), we see that

$$\nu_{(F)} = \nu_{(f)} + \text{tr}\,(\frac{\partial V}{\partial x} E). \tag{3.25}$$

Applying equation (3.17) to F on Γ, we obtain

$$\begin{aligned} M_{(F)} &= Q_F Q^{-1} + Q \frac{\partial F}{\partial x}^{[m+2]} Q^{-1} - \nu_{(F)} I \\ &= Q_f Q^{-1} + Q\Big(\frac{\partial f}{\partial x} + E\frac{\partial V}{\partial x}\Big)^{[m+2]} Q^{-1} - (\nu_{(f)} + \text{tr}\,(\frac{\partial V}{\partial x} E))I. \end{aligned} \tag{3.26}$$

This allows us to reformulate each of the theorems in Section 3.3. We rewrite only Theorem 3.14 and Theorem 3.17.

Theorem 3.18. *If (H4), (H5) and (H6) are satisfied and there exists Q and E such that $\bar{q}_{m+2}(f, Q, E) < 0$ then the unique equilibrium $\bar{x}$ is globally asymptotically stable.*

Theorem 3.19. *Let $D \subseteq \Gamma$ be a compact, simply connected set with boundary ∂D. Suppose D is positively invariant under (3.2) and that the only equilibrium in D is $P \in \partial D$. Further, suppose that P is locally asymptotically stable in Γ and is the only omega limit point in ∂D. If there exist Q and E such that*

$$\mu\big(M_{(F)}\big) < 0$$

on D, then all solutions beginning in D limit to P.

Remark. Since equations (3.2) and (3.23) describe the same behaviour on Γ, the stability of solutions relative to the dynamics in Γ is the same for the two systems. The purpose of considering systems of the form given by (3.23) is to facilitate calculations. Since there are an infinite number of systems that behave the same on Γ, it is quite likely that the original system being studied is not the system for which the calculations are the most straightforward.

3.5 Results of Busenberg and van den Driessche

We now present a theorem and corollary by Busenberg and van den Driessche [8] which are useful in ruling out periodic solutions to differential equations on two dimensional manifolds embedded in $\mathbb{R}^3$. The proofs are based on Stokes' Theorem.

Theorem 3.20. *Let $f : \mathbb{R}^3 \to \mathbb{R}^3$ be a Lipschitz continuous vector field and let ψ be a simple closed piecewise smooth curve which is the boundary of an orientable smooth surface $\varphi \subset \mathbb{R}^3$. Suppose that $g : \mathbb{R}^3 \to \mathbb{R}^3$ is defined and smooth in a neighbourhood of φ, and that it satisfies*

$$g\big(\psi(u)\big) \cdot f\big(\psi(u)\big) \leq 0$$

for all $u \in \partial\varphi$ and $(\operatorname{curl} g) \cdot n \geq 0$ on φ with $(\operatorname{curl} g) \cdot n > 0$ for some point on φ, where n is the unit normal to φ. Then ψ is not the finite union of solution trajectories of (3.2) which are traversed in the positive sense relative to the direction of n.

Corollary 3.21. *Let $\varphi \subset \mathbb{R}^3$ be a smooth orientable surface such that any piecewise smooth simple closed curve ψ in φ is the boundary of a surface $\tilde{\varphi} \subset \varphi$. If $g : \mathbb{R}^3 \to \mathbb{R}^3$ is smooth, $f : \psi \to \mathbb{R}^3$ is Lipschitz, and f and g satisfy*

$$g\big(\psi(u)\big) \cdot f\big(\psi(u)\big) = 0 \tag{3.27}$$

and

$$(\operatorname{curl} g) \cdot n > 0 \quad \text{on } \varphi \tag{3.28}$$

where n is the unit normal to φ, then ψ is not a phase polygon of (3.2).

CHAPTER 4

Stability for Three-Dimensional Homogeneous Systems

4.1. Introduction

A function f is *homogeneous* of degree r if $f(\alpha X) = \alpha^r f(X)$ for all scalars α. Consider the differential equation

$$X' = f(X) \tag{4.1}$$

where $f : \mathbb{R}^3 \to \mathbb{R}^3$ is C^1 and homogeneous of degree 1. Typically, there are no fixed points of (4.1). It is possible, however, to radially project the dynamics described by (4.1) onto a two-dimensional surface. Under the projected dynamics on this surface, there generally are fixed points. These fixed points correspond to exponential solutions to (4.1) which move along a straight line through the origin.

In [34], Li studies equation (4.1) with $f(X) = AX + (\text{diag}X)\phi(X)$ where $A = (a_{ij})_{3\times 3}$ satisfies $a_{ij} \geq 0$ for $i \neq j$ and ϕ is homogeneous of degree 0. The dynamics in the positive orthant are projected onto the surface $\Gamma = \{(X_1, X_2, X_3) \in \mathbb{R}^3_{\geq 0} : X_1 + X_2 + X_3 = 1\}$. It is shown that if $\sum_{i=1}^3 X_i \frac{\partial \phi_i}{\partial X_i} < 0$ then under the projected dynamics, there are no periodic solutions in Γ. In [9], Busenberg and van den Driessche show that if $\frac{\partial \phi_i}{\partial X_i} + \frac{\partial \phi_j}{\partial X_j} - \frac{\partial \phi_i}{\partial X_j} - \frac{\partial \phi_j}{\partial X_i} \leq 0$ for $i \neq j$ then under the projected dynamics, there are no closed phase polygons in Γ. A Bendixson-Dulac criterion for three-dimensional homogeneous systems is also given by Hadeler in [16].

We follow the approach of Li, but work with a more general form for f. In Section 4.2, conditions are given for f which imply that under the projected dynamics, every omega limit set must contain an equilibrium. These conditions

are applied to a class of disease models in Section 4.3. This example includes SEI, SEIS, SIR and SIRS models as well as a model of differential infectivity with two infective classes.

4.2. A Stability Result

Consider the following system of differential equations

$$\begin{aligned} X_1' &= P_1(X_2, X_3, N) + X_1 Q_1(X_2, X_3, N) + X_1 R(X_1, X_2, X_3, N, t) \\ X_2' &= P_2(X_1, X_3, N) + X_2 Q_2(X_1, X_3, N) + X_2 R(X_1, X_2, X_3, N, t) \\ X_3' &= P_3(X_1, X_2, N) + X_3 Q_3(X_1, X_2, N) + X_3 R(X_1, X_2, X_3, N, t) \end{aligned} \tag{4.2}$$

where $N = X_1 + X_2 + X_3$. This yields

$$\begin{aligned} N' &= \sum_{k=1}^{3} \Big(P_k(X, N) + X_k Q_k(X, N) + X_k R(X, N) \Big) \\ &= NR + \sum_{k=1}^{3} \Big(P_k + X_k Q_k \Big). \end{aligned}$$

Consider the following hypotheses.

(H1) For $j = 1, 2, 3$, P_j and Q_j are homogeneous of degrees 1 and 0 respectively.

(H2) The function $\nu(X) = -\sum_{j=1}^{3} \Big(P_j(X, N) + X_j Q_j(X, N) \Big)$ has no explicit dependence on N.

(H3) The non-negative octant $\mathbb{R}^3_{\geq 0}$ is positively invariant.

Note that no assumptions are made about the form of R, the radial component of the vector field. Define proportional variables by letting $x_j = X_j / N$. Then

$$\begin{aligned} x_j' &= \frac{X_j' N - X_j N'}{N^2} \\ &= \frac{X_j'}{N} - x_j \frac{N'}{N} \\ &= \frac{1}{N}(P_j + X_j Q_j + X_j R) - x_j \frac{1}{N} \Big(NR + \sum_{k=1}^{3} (P_k + X_k Q_k) \Big). \end{aligned} \tag{4.3}$$

We now introduce the following hypothesis.

(H4) $\frac{1}{N}P_1(X_2, X_3, N) = P_1(x_2, x_3, 1)$ has no dependence on the third argument and analogous conditions hold for P_2, P_3.

Define $p_j(x) = \frac{1}{N}P_j(X, N)$ and $q_j(x) = Q_j(X, N)$. These are well defined when (H1) holds. We rewrite (4.3) as

$$x_j' = p_j(x) + x_j q_j(x) - x_j \sum_{k=1}^{3} \Big(p_k(x) + x_k q_k(x) \Big) \qquad \text{for } j = 1, 2, 3 \tag{4.4}$$

where p_j and q_j have no dependence on x_j.

Note that (H1) implies that the right-hand side of equation (4.2) can be written as the sum of a homogeneous vector field of degree 1 and a radial vector field. Equation (4.4) is the radial projection of (4.2) onto the plane $\tilde{\Gamma} = \{x : V(x) = 0\}$ where $V = x_1 + x_2 + x_3 - 1$. Thus, the radial component R of (4.2) projects out. We are interested in the behaviour of (4.4) in the simplex $\Gamma = \tilde{\Gamma} \cap \mathbb{R}^3_{\geq 0}$. Hypothesis (H3) implies Γ is positively invariant.

Observe that $V' = \nu(x)V$. Let $U = \frac{1}{x_1 x_2 x_3}$. With the aim of applying results from Section 3.3, we are interested in the quantity $M = U'U^{-1} + U\frac{\partial f}{\partial x}^{[3]}U^{-1} - \nu(x)$ where $\frac{\partial f}{\partial x}^{[3]}$ is the third additive compound [see Appendix A] of the Jacobian matrix. Since (4.4) is a three dimensional system, $\frac{\partial f}{\partial x}^{[3]} = \text{tr}\,(\frac{\partial f}{\partial x})$, the trace of $\frac{\partial f}{\partial x}$. We find

$$\begin{aligned} M &= -\sum_{j=1}^{3} \frac{x_j'}{x_j} + \text{tr}\,(\frac{\partial f}{\partial x}) - \nu(x) \\ &= -\sum_{j=1}^{3} \frac{p_j + x_j q_j + x_j \nu}{x_j} + \sum_{j=1}^{3} \frac{\partial}{\partial x_j}\Big(p_j + x_j q_j + x_j \nu \Big) - \nu \\ &= -\sum_{j=1}^{3} \frac{p_j}{x_j} + \sum_{j=1}^{3} x_j \frac{\partial \nu}{\partial x_j} - \nu. \end{aligned} \tag{4.5}$$

By (H1) and (H2), $\nu(x)$ is homogeneous of degree 1. Hence,

$$\nu(\alpha x_1, \alpha x_2, \alpha x_3) = \alpha\, \nu(x_1, x_2, x_3) \tag{4.6}$$

for any scalar α. Following [34], and differentiating (4.6) with respect to α at $\alpha = 1$ we obtain

$$\sum_{j=1}^{3} \frac{\partial \nu(x)}{\partial x_j} x_j = \nu(x).$$

Thus (4.5) can be written as

$$\begin{aligned} M &= -\sum_{j=1}^{3} \frac{p_j(x)}{x_j} \\ &= -\sum_{j=1}^{3} \frac{\frac{1}{N} P_j(X, N)}{\frac{X_j}{N}} \\ &= -\sum_{j=1}^{3} \frac{P_j(X, N)}{X_j}. \end{aligned} \tag{4.7}$$

Note that since M is a scalar, we can take $\mu(M) = M$.

Suppose $M < 0$ on $\operatorname{int}\Gamma$ and suppose that $\gamma \subset \operatorname{int}\Gamma$ is the trace of a periodic solution to equation (4.4). By Corollary 3.16, γ is orbitally asymptotically stable. Let N_1 be a positively invariant neighbourhood of γ which is attracted to γ and let N_2 be the region bounded by γ. Then $N = N_1 \cup N_2$ is simply connected. Since γ is orbitally asymptotically stable, we see that N contains a compact set K which is attracting in N and contains γ. On the other hand, Theorem 3.13 implies that since $M < 0$, K contains no invariant simple closed curves. This contradicts the fact that γ is the trace of a periodic solution. Thus, there can be no periodic solutions in the interior of Γ.

Since the boundary of Γ does not contain any smooth simple closed curves, there are no periodic solutions which lie entirely in the boundary of Γ. Suppose there is a periodic solution to (4.4) which intersects the interior of Γ at y_1 and

the boundary of Γ at y_2. Then $x(t_0; y_1) = y_2$ for some $t_0 > 0$. Let $\tilde{N} \subset \Gamma$ be a neighbourhood of y_1. Then $x(t_0; \tilde{N})$ is a neighbourhood of y_2. This means $x(t_0; \tilde{N})$ is not a subset of Γ and so Γ is not positively invariant. On the other hand, if hypothesis (H3) holds, then Γ must be positively invariant. We make the following conclusion.

Proposition 4.1. *Suppose system (4.2) satisfies (H1), (H2), (H3) and (H4). If $M < 0$ on $\mathbb{R}^3_{>0}$, then there are no periodic solutions to (4.4) in Γ.*

Since Γ admits a Poincare-Bendixson property, every omega limit set in Γ must either contain an equilibrium or be a periodic orbit. Combining this observation with Proposition 4.1 gives the following result.

Proposition 4.2. *Suppose system (4.2) satisfies (H1), (H2), (H3) and (H4). If $M < 0$ on $\mathbb{R}^3_{>0}$, then under the flow (4.4), every omega limit set in Γ contains an equilibrium.*

If equation (4.4) is uniformly persistent, then the interior of Γ contains a compact set which is absorbing relative to the interior. Applying Theorem 3.13 gives the following result.

Theorem 4.3. *Suppose system (4.2) satisfies (H1), (H2), (H3) and (H4). If (4.4) is uniformly persistant, then each solution of (4.4) limits to an equilibrium.*

Proof. By Theorem 3.13, each solution of (4.4) which intersects the interior of Γ limits to an equilibrium. Suppose a solution is contained in the boundary of Γ which is a triangle. Then the solution must limit to an equilibrium since the boundary of Γ contains no smooth simple closed curves, and hence no periodic orbits. □

4.3. An Example

We now consider, as an example, a model of a disease with two infectious classes I_1 and I_2, as well as a susceptible class S. Proportional mixing is assumed, so that the number of new infections per unit time is $\Delta = \beta_1 \frac{I_1}{N} S + \beta_2 \frac{I_2}{N} S$. We assume that at least one of β_1 and β_2 is positive. To accommodate a large class of models, we allow that newly infected individuals may enter either infectious class, and that there may be movement between the two infectious classes as well as recovery to the susceptible class. Let $\sigma_j \in [0,1]$ be the probability that newly infected individuals enter class I_j with $\sigma_1 + \sigma_2 = 1$. The rate at which individuals leave class I_j for the other infectious class is k_j. The recovery rate is r_j and the disease related death rate is μ_j. Disease independent death occurs at rate d and may be time-dependent. We also assume that vertical transmission happens from I_j into I_j with probability γ_j. The differential equation which describes the model is

$$
\begin{aligned}
I_1' &= b\gamma_1 I_1 + \sigma_1\Big(\beta_1 \frac{I_1}{N} + \beta_2 \frac{I_2}{N}\Big) S + k_2 I_2 - (k_1 + r_1 + \mu_1 + d) I_1 \\
I_2' &= b\gamma_2 I_2 + \sigma_2\Big(\beta_1 \frac{I_1}{N} + \beta_2 \frac{I_2}{N}\Big) S + k_1 I_1 - (k_2 + r_2 + \mu_2 + d) I_2 \\
S' &= b\Big((1-\gamma_1) I_1 + (1-\gamma_2) I_2 + S\Big) + r_1 I_1 + r_2 I_2 - \Big(\beta_1 \frac{I_1}{N} + \beta_2 \frac{I_2}{N}\Big) S - dS.
\end{aligned}
\tag{4.8}
$$

Remarks. (1) By choosing $r_1 = \beta_1 = \gamma_1 = \mu_1 = k_2 = \sigma_2 = 0$, $\sigma_1 = 1$ and $(S, I_1, I_2) = (S, E, I)$, we obtain a SEIS model. If we also choose $r_2 = 0$ then we have the SEI model which has been used by Gao et al. to model fox-rabies [15]. (2) By choosing $r_1 = \beta_2 = \mu_2 = k_2 = \gamma_2 = \sigma_2 = 0$, $\sigma_1 = 1$ and $(S, I_1, I_2) = (S, I, R)$, we obtain a SIRS model. By also choosing $r_2 = 0$, we obtain the SIR model studied by Hethcote in [22]. The SIR model can be used to model measles, mumps and rubella.

(3) Choosing $k_1 = k_2 = \gamma_1 = \gamma_2 = 0$ gives a model of differential infectivity similar to that used by Hyman et al. in [27] to model HIV.

Letting $(X_1, X_2, X_3) = (I_1, I_2, S)$, equation (4.8) can be written in the form of equation (4.2) by defining

$$P_1 = \sigma_1\beta_2\frac{I_2 S}{N} + k_2 I_2 \qquad Q_1 = \sigma_1\beta_1\frac{S}{N} + b\gamma_1 - (k_1 + r_1 + \mu_1)$$

$$P_2 = \sigma_2\beta_1\frac{I_1 S}{N} + k_1 I_1 \qquad Q_2 = \sigma_2\beta_2\frac{S}{N} + b\gamma_2 - (k_2 + r_2 + \mu_2)$$

$$P_3 = b\big((1-\gamma_1)I_1 + (1-\gamma_2)I_2\big) + r_1 I_1 + r_2 I_2 \qquad Q_3 = b - \left(\beta_1\frac{I_1}{N} + \beta_2\frac{I_2}{N}\right)$$

$$R = -d.$$

Then (H1), (H2), (H3) and (H4) are satisfied and (4.7) yields

$$M = -\Big[\sigma_1\beta_2\frac{I_2}{N}\frac{S}{I_1} + k_2\frac{I_2}{I_1} + \sigma_2\beta_1\frac{I_1}{N}\frac{S}{I_2} + k_1\frac{I_1}{I_2} + b(1-\gamma_1)\frac{I_1}{S} + r_1\frac{I_1}{S} + b(1-\gamma_2)\frac{I_2}{S} + r_2\frac{I_2}{S}\Big].$$

If any of $\sigma_1\beta_2$, $\sigma_2\beta_1$, k_j, r_j, or $b(1-\gamma_j)$ is non-zero, then M is negative on $\mathbb{R}^3_{>0}$ and so, by Proposition 4.2, when considering the proportional variables, the omega limit set of each trajectory contains an equilibrium.

If, furthermore, system (4.8) is uniformly persistent, then by then by Theorem 4.3 we may conclude that for the proportional variables, each trajectory limits to a single equilibrium. The dyanamics described by (4.8) will be uniformly persistent for some parameter values, but not all.

4.4. Summary

A test for homogeneous systems has been developed. When applicable, this test shows that the projection of the dynamics onto the simplex, produces a system

for which every omega limit set contains an equilibrium. It is shown that the original system need not be strictly homogeneous, but may be the sum of a homogeneous component and a radial component. The radial component may be time dependent.

The test is applied to an example which includes some standard epidemiological models.

CHAPTER 5

A Model of the Interaction of a Gene and an Infectious Disease

5.1 Introduction

It is well known that susceptibility to malaria is affected by the gene that causes sickle-cell anemia [6]. A similar interaction has been discovered in the relationship between typhoid fever and the gene which causes cystic fibrosis [49].

If an individual has two copies of a particular gene, then the individual develops cystic fibrosis which, in the absence of modern medicine, is usually fatal. If this gene imparted no advantage to carriers, then its frequency in the population would be expected to decline to zero. However, amongst people of European descent, the gene is found in between four and five per cent of the population.

Typhoid fever, a diarrheal disease that once killed about fifteen per cent of those infected, is initiated when the *Salmonella typhi* bacteria enter the gastrointestinal epithelial cells. It has been shown that *Salmonella typhi* have trouble entering the gastrointestinal epithelial cells of individuals who carry the cystic fibrosis gene [49]. If an individual has a single copy of this particular gene, then the individual is partially protected against typhoid fever.

In [5], Beck models cystic fibrosis in the United States, studying the assumption that carriers of the cystic fibrosis gene have an increased fertility rate. It is shown that this is sufficient to keep the gene from dying out of the population. In [6], Beck et al. study a model for the interaction of a gene and an infectious disease. It is assumed that the difference between the genotypes is small enough that singular perturbation methods can be applied. It is shown that solutions go to a slow manifold of dimension one. Movement along this manifold corresponds to

the genetic makeup of the population varying due to the selective pressure brought about by the gene. This is done for infectious diseases of type SIS, SIR and SIRS. Kemper [29] and Longini [44] each study the interaction of an endemic infectious disease with a gene which affects fitness.

We present, in this chapter, models of the population dynamics which arise from an interaction between a gene at a single locus and an infectious disease. For simplicity, we work with SIS type models and ignore stochastic effects. The analysis allows for substantial differences between the genotypes, involving cases where singular perturbation methods do not apply.

In Section 5.2, a general model similar to that studied in [6], is presented. In Section 5.3 the special case where the gene has no effect on the infectious disease is analyzed, yielding the standard SI model. In Section 5.4, we study the case where there is no infectious disease. This results in the standard model of a neutral gene in a population. In Sections 5.5 and 5.6, we present new work in which we study non-trivial interactions between the gene and the infectious disease. The cases that are dealt with in Sections 5.5 and 5.6 are the special case when heterozygotes are immune to the disease and homozygotes die, and the special case when homozygotes and heterozygotes are both immune to the disease, respectively.

5.2 Formulation of the General Model

The population N is split into three groups N_0, N_1 and N_2 where N_j consists of those individuals who carry j copies of the gene in question. Each group N_j is subdivided into those who have the infectious disease I_j and those who do not S_j. Proportional mixing is assumed both for spreading the disease and for reproducing. Individuals are assumed to make an average of c contacts per unit time which

could potentially transmit the infectious disease. A fraction I_k/N of these are with individuals in class I_k. Let β_j be the probability that a contact between a susceptible in class S_j and an infective results in a new infection. Then the force of infection on class S_j is $c\beta_j(I_1 + I_2 + I_3)/N$. The birth rate is b and the natural death rate is d. The disease related death rate for class I_j is μ_j. The rate at which individuals recover from I_j to S_j is r_j. We assume no vertical transmission of the infectious disease, meaning that the recruitment of new individuals is into the susceptible classes. Let Q_j be the probability that a newborn is born into class S_j. This yields the following flow diagram.

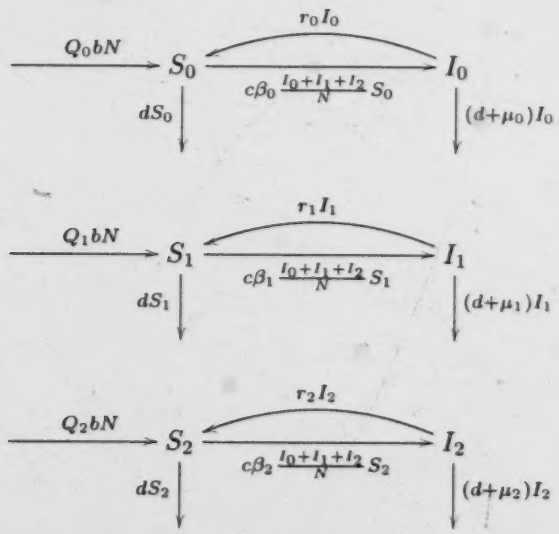

Figure 5.1: Transfer diagram for the general genetic model.

The probabilities Q_j are functions of the variables $n_j = N_j/N$ which represent the probability that a person is in class N_j. The probability p that a child receives the gene being studied from a particular parent, say the father, is the sum over $j = 0, 1, 2$ of the probability that the father has j copies of the gene times the

probability that he will pass a copy of it on. Thus,

$$\begin{aligned} p &= 0 \cdot n_0 + \frac{1}{2} \cdot n_1 + 1 \cdot n_2 \\ &= \frac{1}{2} n_1 + n_2. \end{aligned} \tag{5.1}$$

The probability that a child does not receive the gene from a particular parent is $1 - p = n_0 + \frac{1}{2} n_1$. Since each child has two parents we obtain $Q_0 = (1-p)^2$, $Q_1 = 2p(1-p)$ and $Q_2 = p^2$. Note that p also represents the frequency of the gene in the population.

We will be interested in the fractions of the population that are in each group. These fractions are given by $s_j = S_j/N$ and $i_j = I_j/N$ for $j = 0, 1, 2$. We proceed by analyzing several special cases.

5.3 The Case with No Genetics

Consider an infectious disease in the absence of any genetic effects. Then $N = S_0 + I_0$ and $S_j = I_j = 0$ for $j = 1, 2$. Then $Q_0 = 1$. The transfer diagram is as follows.

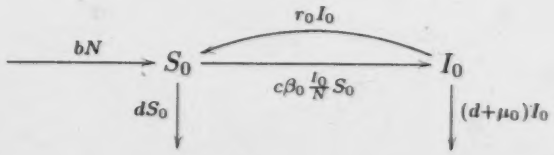

Figure 5.2: Transfer diagram for the SI model with no genetics.

The differential equations to describe the sizes of the groups are

$$\begin{aligned} S_0' &= bN - c\beta_0 \frac{I_0}{N} S_0 - dS_0 + r_0 I_0 \\ I_0' &= c\beta_0 \frac{I_0}{N} S_0 - (d + \mu_0 + r_0) I_0 \\ N' &= (b-d)N - \mu_0 I_0. \end{aligned}$$

For the proportional variables, noting that $i_0 = 1 - s_0$ we get

$$\begin{aligned} s_0' &= \frac{S_0'N - S_0N'}{N^2} \\ &= \frac{1}{N}S_0' - s_0\frac{N'}{N} \\ &= b - c\beta_0 i_0 s_0 - ds_0 + r_0 i_0 - s_0\big(b - d - \mu_0 i_0\big) \\ &= \Big(b + r_0 - c\beta_0 s_0 + \mu_0 s_0\Big)\big(1 - s_0\big). \end{aligned} \tag{5.2}$$

This is a one dimensional system with equilibria at P_0 given by $s_0 = 1$ and P_1 given by $s_0 = \frac{b+r_0}{c\beta_0 - \mu_0}$ if $c\beta_0 \neq \mu_0$, although only the range $s_0 \in [0,1]$ is biologically significant. Analysis of the flow for different cases allows us to conclude that if P_1 is biologically significant then it attracts all solutions except P_0. Otherwise, P_0 is globally stable. Another way to say this, is that the disease dies out if $c\beta_0 - b - r_0 - \mu_0 \leq 0$ and persists, limiting to a constant proportion, otherwise.

5.4 The Case with No Infectious Disease

We consider the situation in which there is a neutral gene in a population which confers neither an advantage nor a disadvantage. In the absence of an infectious disease, we have $I_j = 0$ and $N_j = S_j$. The only change in the population over time will be due to births and deaths. The transfer diagram is as follows

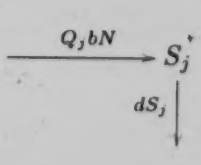

Figure 5.3: Transfer diagram for the genetic model with no disease.

for $j = 1,2,3$ where $Q_0 = (s_0 + \frac{1}{2}s_1)^2$, $Q_1 = 2(s_0 + \frac{1}{2}s_1)(\frac{1}{2}s_1 + s_2)$ and $Q_2 = (\frac{1}{2}s_1 + s_2)^2$. The differential equation which describes the sizes of the population

groups is

$$S_j' = Q_j bN - dS_j \qquad \text{for } j = 1, 2, 3,$$
$$N' = (b - d)N.$$

The differential equation for the proportional variables is

$$\begin{aligned} s_0' &= (s_0 + \frac{1}{2}s_1)^2 b - bs_0 \\ s_1' &= 2(s_0 + \frac{1}{2}s_1)(\frac{1}{2}s_1 + s_2)b - bs_1 \\ s_2' &= (\frac{1}{2}s_1 + s_2)^2 b - bs_2. \end{aligned} \tag{5.3}$$

Consider how p evolves in time. By (5.3), $p' = 0$. This means that since there is no selective pressure related to the gene, its frequency in the population remains constant. The equation for s_2 then, becomes

$$s_2' = b(p^2 - s_2).$$

Thus, s_2 goes to the constant value p^2. Similarly, s_0 and s_1 limit to $(1-p)^2$ and $2p(1-p)$, respectively. Thus for each $p \in [0,1]$ we have an equilibrium with a one dimensional stable manifold in the surface $\Gamma = \{s_0 + s_1 + s_2 = 1\} \cap \mathbb{R}^3_{\geq 0}$. These are called the Hardy-Weinberg equilibria [25] and each solution in Γ limits to exactly one of them.

5.5 Cystic Fibrosis and Typhoid Fever

This model can also be used to the interaction between malaria and sickle-cell anemia. A weakness of such an application, though, comes from the fact that malaria is transmitted via a vector, the mosquito.

For simplicity, we assume that one copy of the gene confers complete immunity to the infectious disease, while those born with two copies of the gene die sufficiently young that they need not be included in the active population for spreading the disease or for reproducing. Thus, $N = S_0 + I_0 + S_1$ and $I_1 = S_2 = I_2 = 0$. The flow diagram for this situation is as follows

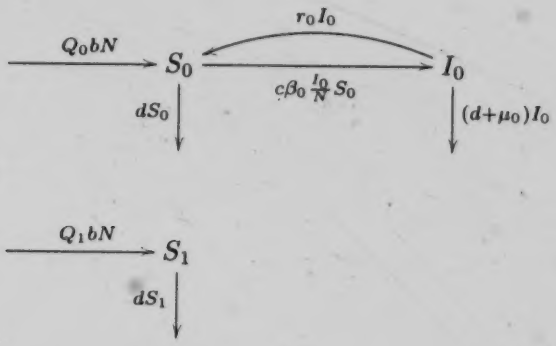

Figure 5.4: Transfer diagram for the model of cystic fibrosis and typhoid fever.

where $Q_0 = (s_0 + i_0 + \frac{1}{2}s_1)^2$ and $Q_1 = s_1(s_0 + i_0 + \frac{1}{2}s_1)$. This yields the following differential equation for the group sizes.

$$
\begin{aligned}
S_0' &= Q_0 bN - c\beta_0 \frac{I_0}{N} S_0 + r_0 I_0 - dS_0 \\
I_0' &= c\beta_0 \frac{I_0}{N} S_0 - (d + \mu_0 + r_0) I_0 \\
S_1' &= Q_1 bN - dS_1 \\
N' &= (Q_0 + Q_1) bN - dN - \mu_0 I_0.
\end{aligned}
$$

Note that the effective birth rate for the total population is $(Q_0 + Q_1)\, b \leq b$ because there will be some newborns with two copies of the gene when both parents have one copy. These newborns are assumed to die and are not included in the model. Suppressing subscripts for r_0, β_0 and μ_0, the equation for the proportional variables

is

$$\begin{aligned} s_0' &= b(1-\frac{1}{2}s_1)^2 - c\beta s_0 i_0 + r i_0 + s_0\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big) \\ i_0' &= c\beta s_0 i_0 - r i_0 - \mu i_0 + i_0\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big) \\ s_1' &= b s_1(1-\frac{1}{2}s_1) + s_1\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big). \end{aligned} \tag{5.4}$$

Let $\Gamma = \{s_0 + i_0 + s_1 = 1\} \cap \mathbb{R}^3_{\geq 0}$.

Theorem 5.1. *If $c\beta - r - b - \mu \leq 0$ then in Γ, $P_0 = (1,0,0)$ is the only equilibrium and is globally stable. If $c\beta - r - b - \mu > 0$ then the equilibria in Γ are given by P_0, $P_1 = (\frac{r+b}{c\beta-\mu}, \frac{c\beta-\mu-r-b}{c\beta-\mu}, 0)$ and $P_2 = (x_*, y_*, z_*)$ where $x_*, y_*, z_* > 0$. When $c\beta - r - b - \mu > 0$, P_2 attracts all solutions in the interior of Γ.*

A proof of this claim can be found in Appendix B.

Thus, if the disease and the gene are present in the population, then they either both die out, or both limit to a constant endemic proportion. Comparing Theorem 5.1 to the conclusion of Section 5.3, we see that the presence of this type of gene has no impact on whether or not the disease persists. We now show that the presence of the gene causes the disease to persist at a lower level in the population.

Let y be the value of i_0 at P_1. Equation (5.4.b) evaluated at P_1 implies

$$0 = c\beta(1-y) - r - \mu + \mu y - b. \tag{5.5}$$

Suppose that $s_1 > 0$ and $i_0 = y + \epsilon$ for some $\epsilon \geq 0$. Substituting $s_0 = 1 - y - \epsilon - s_1$, (5.4.b) yields

$$\frac{i_0'}{i_0} = c\beta(1-y-\epsilon-s_1) - r - \mu + \mu(y+\epsilon) - b + \frac{1}{4}bs_1^2. \tag{5.6}$$

Using (5.5) to simplify (5.6) gives

$$\begin{aligned} \frac{i_0'}{i_0} &= -c\beta(\epsilon + s_1) + \mu\epsilon + \frac{1}{4}bs_1^2 \\ &= (\mu - c\beta)\epsilon + (\frac{1}{4}bs_1 - c\beta)s_1 \end{aligned}$$

which is negative for

$$c\beta - r - b - \mu > 0. \tag{5.7}$$

Thus, if (5.7) holds then $i_0 \geq y$ and $s_1 > 0$ together imply that i_0 is decreasing. Combining this with Theorem 5.1 , we conclude that $y_* < y$. Thus if (5.7) holds, then the disease and the gene both persist in the population but the disease persists at a lower level than it would in the absence of the gene.

5.6 No Genetic Disadvantage

We now consider the case where one or two copies of a gene provide immunity to an infectious disease with no associated disadvantage. In this case, $N = S_0 + I_0 + S_1 + S_2$ and $I_1 = I_2 = 0$. The transfer diagram is

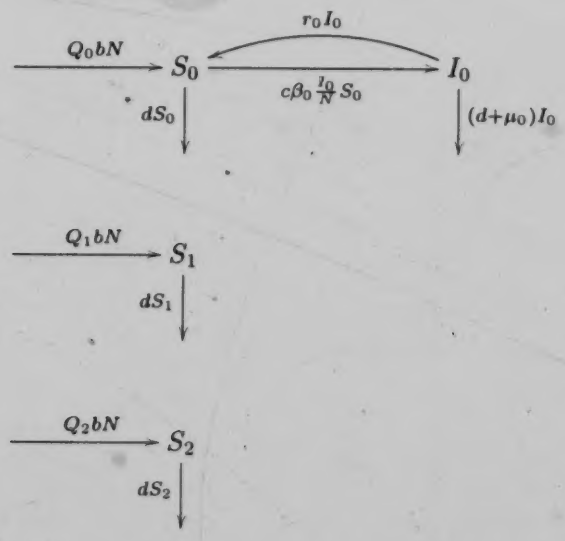

Figure 5.5: Transfer diagram for a model of an infectious disease for which there is genetic immunity.

where $Q_0 = (s_0 + i_0 + \frac{1}{2}s_1)^2$, $Q_1 = 2(s_0 + i_0 + \frac{1}{2}s_1)(\frac{1}{2}s_1 + s_2)$ and $Q_2 = (\frac{1}{2}s_1 + s_2)^2$. The differential equation which describe the sizes of the population groups is

$$\begin{aligned}
S_0' &= Q_0 bN - c\beta_0 \frac{I_0}{N} S_0 + r_0 I_0 - dS_0 \\
I_0' &= c\beta_0 \frac{I_0}{N} S_0 - (d + \mu_0 + r_0) I_0 \\
S_1' &= Q_1 bN - dS_1 \\
S_2' &= Q_2 bN - dS_2 \\
N' &= (b - d)N - \mu_0 I_0.
\end{aligned}$$

Suppressing subscripts for r_0, β_0 and μ_0, the equation for the proportional variables is

$$\begin{aligned}
s_0' &= b(s_0 + i_0 + \frac{1}{2}s_1)^2 - c\beta s_0 i_0 + r i_0 - b s_0 + \mu i_0 s_0 \\
i_0' &= c\beta s_0 i_0 - (r + b + \mu) i_0 + \mu i_0^2 \\
s_1' &= 2b(s_0 + i_0 + \frac{1}{2}s_1)(\frac{1}{2}s_1 + s_2) - b s_1 + \mu i_0 s_1 \\
s_2' &= b(\frac{1}{2}s_1 + s_2)^2 - b s_2 + \mu i_0 s_2.
\end{aligned} \tag{5.8}$$

When $i_0 = 0$, this system reduces to (5.3) and solutions limit to one of the Hardy-Weinberg equilibria given by $(s_0, i_0, s_1, s_2) = ((1-p)^2, 0, 2p(1-p), p^2)$ where $p \in [0, 1]$ represents the frequency of the gene in the population.

Observe how p evolves in the population when the infectious disease is present. By (5.1) and (5.8), $p' = \mu i_0 p$. Thus, if $i_0, p > 0$ then p increases until i_0 is zero. Since p is bounded above by 1, this means that the disease must die out. Therefore all solutions approach the Hardy-Weinberg equilibria. Since p is non-decreasing, each solution goes to a unique Hardy-Weinberg equilibrium.

5.7 Conclusions

In the absence of selective pressure and stochastic effects, the prevalence of a gene in a population remains constant and the proportions of the population in each of the genotypes go to the proportions given by one of the Hardy-Weinberg equilibria.

If individuals with one or two copies of the gene are protected from infection, then the disease dies out and each trajectory goes to a Hardy-Weinberg equilibrium.

If one copy of the gene provides immunity to the infectious disease, while two copies of the gene is fatal, then the disease will persist in the population if and only if it is able to persist in the absence of the gene. If the disease does persist, then the proportion of the population which is infected will be smaller than it would be in the absence of the gene.

CHAPTER 6

Differential Infectivity

6.1 Introduction

Between individuals infected with HIV, viral loads in the chronic phase may differ by many orders of magnitude. Those individuals with high viral loads in the chronic phase tend to develop Acquired Immune Deficiency Syndrome (AIDS) more rapidly, whereas those with lower viral loads progress more slowly or not at all [4, 10, 48, 58]. It is also thought that viral load correlates well with infectiousness [27].

In [27], Hyman et al. present the following system which models the fact that different people react to a disease differently. This phenomenon is called differential infectivity.

The population being studied is divided into a susceptible class S and infective classes $I_1, \ldots, I_n$. The different infective subgroups are meant to reflect differences in viral loads. The total population is given by $N = S + I_1 + \cdots + I_n$. The transfer diagram is as follows.

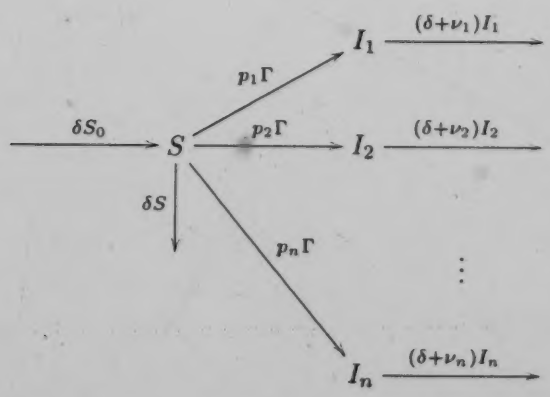

Figure 6.1: Transfer diagram for a model of differential infectivity.

People are removed from the population for non-disease related reasons (including death, migration and changes in sexual behaviour) at a rate δ. There is constant recruitment δS_0 so that in the absence of disease, the population stabilizes at the level S_0. Individuals leave infectious class I_j due to HIV related illnesses or a positive HIV test at a rate $\nu_j > 0$. We assume, without loss of generality, that $\nu_1 \leq \ldots \leq \nu_n$.

It is assumed that a susceptible individual has c contacts per unit time. A proportion $\frac{I_j}{N}$ of these contacts are with individuals in class I_j. A fraction β_j of these contacts will result in a new infection, so that the incidence is $\Gamma = \sum_{j=1}^{n} c\beta_j \frac{I_j}{N} S$. Upon infection, an individual enters infectious class I_k with probability $p_k > 0$. The difference between the infective subgroups may be in either the infectivity β_j or in the disease-related death rate ν_j.

The differential equation for the sizes of the population subgroups is

$$\frac{dS}{dt} = \delta(S_0 - S) - \sum_{j=1}^{n} c\beta_j \frac{I_j}{N} S$$

$$\frac{dI_k}{dt} = p_k \sum_{j=1}^{n} c\beta_j \frac{I_j}{N} S - (\delta + \nu_k) I_k \qquad k = 1, ..., n.$$

The authors calculate the reproductive ratio to be

$$R_0 = \sum_{j=1}^{n} \frac{c\beta_j p_j}{\delta + \nu_j}.$$

It is determined that if $R_0 < 1$ then the disease-free equilibrium $P_0 = (S_0, 0, \ldots, 0)$ is locally asymptotically stable. On the other hand, if $R_0 > 1$, then P_0 is unstable and there is a unique endemic equilibrium which is locally asymptotically stable. In neither case is global stability shown.

In [28], Kemper studies two models of differential infectivity with two infective groups. The purpose of the analysis is to determine how to detect, by observing

data, the presence of a subgroup in the population which is highly infective. It is shown that for a SIS model with two infective classes, non-monotone behaviour may occur while it cannot occur when there is only a single infective class. The models differ substantially from the model found in [27] and the model presented here.

We now present a model of differential infectivity which differs from the model in [27] in that the incidence is determined by mass action rather than proportional mixing. For this new model, we determine the threshold parameter R_0. For $R_0 < 1$, the only fixed point is the disease-free equilibrium which is locally asymptotically stable. For $R_0 > 1$, there is a unique endemic equilibrium which is locally asymptotically stable. Global stability is demonstrated for a subset of the parameter space using the techniques of Li and Muldowney described in Section 3.2.

6.2 Model Formulation

It is assumed that a susceptible individual has cI_j contacts with individuals in class I_j per unit time. A fraction β_j of these contacts will result in a new infection, so that the incidence is $\Gamma = \sum_{j=1}^{n} c\beta_j I_j S$. In all other respects, this model is the same as that described in the previous section.

The differential equation for the sizes of the population subgroups is

$$\begin{aligned} \frac{dS}{dt} &= \delta(S_0 - S) - \sum_{j=1}^{n} c\beta_j I_j S \\ \frac{dI_k}{dt} &= p_k \sum_{j=1}^{n} c\beta_j I_j S - (\delta + \nu_k) I_k \qquad k = 1, ..., n \end{aligned} \tag{6.1}$$

Note that the positive orthant is positively invariant. Also, note that

$$N' = \delta(S_0 - N) - \sum_{k=1}^{n} \nu_k I_k. \tag{6.2}$$

Thus, asymptotically, all solutions enter the compact set $0 \leq N \leq S_0$. We now study the dynamics described by equation (6.1).

6.3 The Disease-Free Equilibrium

For all values of the model parameters, the disease-free equilibrium P_0 is given by $(S, I_1, \ldots, I_n) = (S_0, 0, \ldots, 0)$. Stability is determined by studying the Jacobian matrix

$$\frac{\partial f}{\partial x} = \begin{bmatrix} -\delta - \sum_{j=1}^{n} c\beta_j I_j & -c\beta_1 S & \ldots & -c\beta_n S \\ p_1 \sum_{j=1}^{n} c\beta_j I_j & p_1 c\beta_1 S - (\delta + \nu_1) & \ldots & p_1 c\beta_n S \\ \vdots & \vdots & \ddots & \vdots \\ p_n \sum_{j=1}^{n} c\beta_j I_j & p_n c\beta_1 S & \ldots & p_n c\beta_n S - (\delta + \nu_n) \end{bmatrix}.$$

To be clear about the entries in the matrix $\frac{\partial f}{\partial x}$ we note that the $(i+1, j+1)$ entry is $p_i c\beta_j$ for $i, j = 2, \ldots, n+1$, $i \neq j$ and the $(i+1, i+1)$ entry is $p_i c\beta_j - (\delta + \nu_i)$ for $i = 2, \ldots, n+1$. Following the approach used by Hyman et al. in Appendix B of [27], we let

$$Q_1 = \begin{bmatrix} 1 & 0 & \ldots & 0 \\ p_1 & 1 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ p_n & 0 & \ldots & 1 \end{bmatrix}$$

and perform the similarity transformation $M_1 = Q_1 \frac{\partial f}{\partial x} Q_1^{-1}$ to get a simpler matrix with the same eigenvalues as $\frac{\partial f}{\partial x}$. Explicitly,

$$M_1 = \begin{bmatrix} -\delta + \sum_{j=1}^{n} c\beta_j (p_j S - I_j) & -c\beta_1 S & \ldots & -c\beta_n S \\ p_1 \nu_1 & -(\delta + \nu_1) & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ p_n \nu_n & 0 & \ldots & -(\delta + \nu_n) \end{bmatrix} \tag{6.3}$$

where the lower right $n \times n$ block is diagonal. This matrix will be used for local and global stability analysis. At P_0,

$$M_1 = \begin{bmatrix} -\delta + \sum_{j=1}^{n} c\beta_j p_j S_0 & -c\beta_1 S_0 & \ldots & -c\beta_n S_0 \\ p_1 \nu_1 & -(\delta + \nu_1) & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ p_n \nu_n & 0 & \ldots & -(\delta + \nu_n) \end{bmatrix}.$$

Suppose $\nu_j \neq \nu_k$ for $j \neq k$. Let $u = [u_0, \ldots, u_n]^T$ be an eigenvector of M_1 at P_0 with corresponding eigenvalue λ. Then $M_1 u = \lambda u$. The bottom n rows of this equation yield $u_j = \frac{p_j \nu_j}{\delta + \nu_j + \lambda} u_0$. In order to get a non-zero eigenvector, we assume that $u_0 \neq 0$. Substituting into the top row and canceling u_0 from each side gives

$$-\delta + \sum_{j=1}^{n} c\beta_j p_j S_0 - \sum_{j=1}^{n} c\beta_j S_0 \frac{p_j \nu_j}{\delta + \nu_j + \lambda} = \lambda. \tag{6.4}$$

Define $f(\lambda)$ to be the left hand side of (6.4). Then we are interested in finding intersections of the graphs of $f(\lambda)$ and the identity map. Considering one sided limits, we see that $\lim_{\lambda \to -(\delta+\nu_j)^+} f(\lambda) = -\infty$ and $\lim_{\lambda \to -(\delta+\nu_j)^-} f(\lambda) = \infty$. Since the ν_j are distinct, there must be at least one solution to (6.4) in each interval $(-(\delta + \nu_j), -(\delta + \nu_{j-1}))$ for $j = 2, \ldots, n$. We label these eigenvalues as $\lambda_2, \ldots, \lambda_n$. Let λ_0 and λ_1 be the remaining eigenvalues.

Note that if the ν_j are not all distinct, then by considering a perturbation of the parameters and using the continuous dependence of eigenvalues on matrix elements, we can show that there are $n - 1$ eigenvalues in the interval $[-(\delta + \nu_n), -(\delta + \nu_1)]$.

Through expansion by cofactors, it can be shown that at P_0,

$$\det(M_1) = (-1)^n (R_0 - 1)\, \delta \prod_{j=1}^{n} (\delta + \nu_j) \tag{6.5}$$

where

$$R_0 = \sum_{j=1}^{n} \frac{c\beta_j p_j}{\delta + \nu_j} S_0$$

is the reproduction ratio. Since $\operatorname{sgn}(\det M_1) = \operatorname{sgn}(\lambda_0 \cdots \lambda_n)$ and $\lambda_2, \ldots, \lambda_n < 0$, equation (6.5) implies

$$\operatorname{sgn}(\lambda_0 \lambda_1) = \operatorname{sgn}(1 - R_0). \tag{6.6}$$

If $R_0 > 1$ then (6.6) implies that one eigenvalue, say λ_0, is positive and the other λ_1 is negative. In this case, P_0 has a one dimensional unstable manifold and

a n dimensional stable manifold. Since the positive orthant is positively invariant, one branch of the unstable manifold must point into the physically relevant space. Otherwise, there would exist solutions with positive initial conditions which would follow the unstable manifold out of the positive orthant. The other branch of the unstable manifold points in the opposite direction, away from the positive orthant. Similarly, the stable manifold cannot intersect the interior of the positive orthant. To see this, recall that points near an equilibrium which lie on neither the stable manifold nor the unstable manifold tend to the unstable manifold, without intersecting the stable manifold. Since the stable manifold has dimension $n-1$, it partitions sufficiently small neighbourhoods of P_0 into points which lie on the stable manifold, points which tend to the positive branch of the unstable manifold, and points which tend to the other branch of the unstable manifold. If the stable manifold intersected the interior of the positive orthant, then there would be points in the positive orthant which would tend to the branch of the unstable manifold that points away from the positive orthant. This would contradict the fact that the positive orthant is positively invariant.

Suppose $R_0 < 1$. We now show that λ_0 and λ_1 both have negative real part. Note that $f(0) = \delta(R_0 - 1)$, so when $R_0 = 1$, (6.4) is satisfied by $\lambda = 0$. We may also conclude that for $R_0 \neq 1$, λ_0 and λ_1 cannot be zero since equation (6.4) would not be satisfied. Noticing that

$$f'(\lambda) = \sum_{j=1}^{n} \frac{c\beta_j S_0 p_j \nu_j}{(\delta + \nu_j + \lambda)^2}$$

we can show that $f'(0) < 1$ if $R_0 \leq 1$ while the derivative of the right-hand side of (6.4) is one. Thus, as R_0 decreases from one, the solution $\lambda = 0$ to (6.4) moves to the left becoming negative. Thus, (6.6) implies that if R_0 is slightly less than one then λ_0 and λ_1 are both negative and so P_0 is stable. Further, as R_0 continues to

decrease from 1, a real eigenvalue cannot pass through zero since (6.4) would not be satisfied.

We must now show that there is no Hopf bifurcation as R_0 continues to decrease. We look for eigenvalues that are purely imaginary. Assume that $\lambda_0 = \gamma i$ for some $\gamma \neq 0$. Then $\lambda_1 = -\gamma i$ and (6.4) implies

$$\begin{aligned}\gamma i &= -\delta + \sum_{j=1}^{n} c\beta_j p_j S_0 - \sum_{j=1}^{n} c\beta_j p_j S_0 \frac{\nu_j}{\delta + \nu_j + \gamma i} \\ &= -\delta + \sum_{j=1}^{n} c\beta_j p_j S_0 - \sum_{j=1}^{n} c\beta_j p_j S_0 \frac{\nu_j(\delta + \nu_j - \gamma i)}{(\delta + \nu_j)^2 + \gamma^2}.\end{aligned}$$

Taking the imaginary component of this equation and canceling γ from each side, we get

$$\begin{aligned}1 &= \sum_{j=1}^{n} c\beta_j p_j S_0 \frac{\nu_j}{(\delta + \nu_j)^2 + \gamma^2} \\ &= \sum_{j=1}^{n} \frac{c\beta_j p_j S_0}{\delta + \nu_j} \frac{\nu_j(\delta + \nu_j)}{(\delta + \nu_j)^2 + \gamma^2} \\ &< \sum_{j=1}^{n} \frac{c\beta_j p_j S_0}{\delta + \nu_j} \\ &= R_0\end{aligned}$$

which contradicts our assumption that $R_0 < 1$. This means that P_0 cannot lose stability through a Hopf bifurcation as R_0 decreases from one. Thus P_0 is locally asymptotically stable for $R_0 < 1$.

Proposition 6.1. *If $R_0 < 1$ then P_0 is locally asymptotically stable. If $R_0 > 1$ then P_0 is unstable and the only trajectories in the positive orthant which limit to P_0 lie on the disease-free axis.*

Proof. All that remains to be shown is that for $R_0 > 1$, the only points which limit to P_0 lie on the disease-free axis. Suppose $R_0 > 1$. It has already been demonstrated

that the stable manifold does not intersect the interior of the positive orthant. If $I_k = 0$ for $k = 1, \ldots, n$, then I_k' is also zero for each k, and $S' = \delta(S_0 - S)$. Thus, we see that solutions starting on the disease-free axis remain there and limit to P_0. Suppose that a solution begins at some other point on the boundary of the positive orthant. Then $I_j > 0$ for some j. Since S' is positive when $S = 0$, we can assume that S is positive. This means that if $I_k = 0$ then $I_k' > 0$. Thus, if a solution begins at a point on the boundary of the positive orthant, but not on the disease free axis, then the solution moves immediately to the interior. Since the stable manifold of P_0 does not intersect the interior of the positive orthant, trajectories of this type, must not lie in the stable manifold, and therefore they cannot limit to P_0. □

Remarks. (1) Proposition 6.1 can also be proven by using Thieme's Theorem 4.5 of [56].

(2) We present here an alternate proof of the global stability of the P_0 for $R_0 < 1$ suggested by H. W. Hethcote. An advantage of this approach is that it also resolves the global stability of P_0 for $R_0 = 1$.

Let $V = \sum_{k=1}^{n} b_k I_k$, where the coefficients b_k are to be determined. Then

$$\begin{aligned} V' &= \sum_{k=1}^{n} b_k p_k \sum_{j=1}^{n} c\beta_j I_j S - \sum_{k=1}^{n} b_k(\delta + \nu_k) I_k \\ &= \sum_{k=1}^{n} b_k p_k \sum_{j=1}^{n} c\beta_j I_j S - \sum_{k=1}^{n} b_j(\delta + \nu_j) I_j. \end{aligned}$$

Now, let $b_j = c\beta_j/(\delta + \nu_j)$, so that

$$\begin{aligned} V' &= \sum_{k=1}^{n} \frac{c\beta_k p_k S}{\delta + \nu_k} \sum_{j=1}^{n} c\beta_j I_j - \sum_{j=1}^{n} c\beta_j I_j \\ &= \Big(\sum_{k=1}^{n} \frac{c\beta_k p_k S}{\delta + \nu_k} - 1 \Big) \sum_{j=1}^{n} c\beta_j I_j \\ &= \Big(\frac{S}{S_0} R_0 - 1 \Big) \sum_{j=1}^{n} c\beta_j I_j. \end{aligned}$$

By considering equation (6.2), it is clear that $N \leq S_0$ asymptotically. Thus, we may assume that $S \leq S_0$. Therefore, $V' \leq 0$ with equality if and only if $S = S_0$ and $R_0 = 1$ or $I_j = 0$ for $j = 1, \ldots, n$. By the Lyapunov-Lasalle Theorem [31], solutions limit to the largest invariant set for which $V' = 0$. Since $N = S + I_1 + \cdots + I_n \leq S_0$, we see that P_0 is globally stable.

6.4 The Endemic Equilibrium

For $R_0 \leq 1$, P_0 is the only equilibrium in the non-negative orthant. If $R_0 > 1$ then there is a unique endemic equilibrium P_* given by $S = \frac{S_0}{R_0}$, $I_k = p_k \frac{\delta}{\delta + \nu_k}(1 - \frac{1}{R_0})S_0$ for $k = 1, \ldots, n$. At P_*, the transformed Jacobian M_1 is given by

$$\begin{bmatrix} -\delta R_0 + \frac{1}{R_0}\sum_{j=1}^{n} c\beta_j p_j S_0 & -c\beta_1 \frac{S_0}{R_0} & \cdots & -c\beta_n \frac{S_0}{R_0} \\ p_1\nu_1 & -(\delta + \nu_1) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ p_n\nu_n & 0 & \cdots & -(\delta + \nu_n) \end{bmatrix}$$

where the lower right $n \times n$ block is diagonal. The local asymptotic stability of P_* is shown by the same method that was used to show that P_0 was locally asymptotically stable for $R_0 < 1$.

To determine the global stability of (6.1), we consider the linear system

$$y' = M_1 y$$

where $y \in \mathbb{R}^{n+1}$ and M_1 is given by (6.3).

Noticing that the off-diagonal elements of M_1 have opposite signs when compared with their symmetric counterparts, we can transform M_1 to get a matrix whose symmetric part is diagonal. Let $Q = \text{diag}(g_0, \ldots, g_n)$ where $g_j(S, I_1, \ldots, I_n)$

is a real valued function which is never zero, for $j = 0, \ldots, n$. Let

$$\begin{aligned} M &= Q_f Q^{-1} + Q M_1 Q^{-1} \\ &= \operatorname{diag}\left(\frac{g_0'}{g_0}, \ldots, \frac{g_n'}{g_n}\right) \\ &\quad + \begin{bmatrix} -\delta + \sum_{j=1}^n c\beta_j (p_j S - I_j) & -c\beta_1 S \frac{g_0}{g_1} & \ldots & -c\beta_n S \frac{g_0}{g_n} \\ p_1 \nu_1 \frac{g_1}{g_0} & -(\delta + \nu_1) & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ p_n \nu_n \frac{g_n}{g_0} & 0 & \ldots & -(\delta + \nu_n) \end{bmatrix} \end{aligned}$$

where Q_f is the directional derivative of Q in the direction of the vector field f.

In order to make the symmetric part of M into a diagonal matrix, we require that $p_k \nu_k g_k / g_0 = c\beta_k S g_0 / g_k$ for $k = 1, \ldots, n$ and so, we find

$$g_k = g_0 \sqrt{\frac{c\beta_k}{p_k \nu_k}} S^{\frac{1}{2}}$$

where g_0 is, as yet, undetermined.

This gives $g_k'/g_k = \frac{1}{2} S'/S + g_0'/g_0$. We now have

$$\operatorname{sym}(M) = \begin{bmatrix} A_0 & 0 & \ldots & 0 \\ 0 & A_1 & \ldots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \ldots & A_n \end{bmatrix}$$

where $\operatorname{sym}(M)$ is the symmetric part of M, $A_0 = -\delta + \sum_{j=1}^n c\beta_j (p_j S - I_j) + \frac{g_0'}{g_0}$, and $A_k = \frac{1}{2} \frac{S'}{S} - (\delta + \nu_k) + \frac{g_0'}{g_0}$ for $k = 1, \ldots, n$.

In order to show the global stability of (6.1), we only need that $\mu(M^{[2]})$ be negative (on average) for some Lozinskii measure μ. By using $\mu = \mu_2$, the Lozinskii measure associated with the standard Euclidean norm, the problem is reduced to showing that the largest real part of an eigenvalue of the symmetric part of $M^{[2]}$ is negative. It is now useful to note that by properties of additive compound matrices

[see Appendix A], we get

$$\begin{aligned}\operatorname{sym}(M^{[2]}) &= \frac{1}{2}\left(M^{[2]} + M^{[2]^T}\right)\\ &= \frac{1}{2}\left(M + M^T\right)^{[2]}\\ &= \left(\operatorname{sym} M\right)^{[2]}\\ &= \operatorname{diag}(A_0 + A_1, \ldots, A_0 + A_n, A_1 + A_2, \ldots, A_1 + A_n, \ldots, A_{n-1} + A_n).\end{aligned}$$

For $1 \le k \le n$ we have $A_0 + A_k = -(2\delta + \nu_k) + \sum_{j=1}^{n} c\beta_j(p_j S - I_j) + \frac{1}{2}\frac{S'}{S} + 2\frac{g_0'}{g_0}$ and for $1 \le i < k \le n$ we have $A_i + A_k = -(2\delta + \nu_i + \nu_k) + \frac{S'}{S} + 2\frac{g_0'}{g_0}$. Therefore,

$$\mu_2(M^{[2]}) = \operatorname{Max}(A_0 + A_1\,,\ A_1 + A_2).$$

Let $g_0 = S^{-\frac{1}{2}} \prod_{k=1}^{n} I_k^{-a_k}$ for some positive constants a_k, $k = 1, \ldots, n$. Then $g_0'/g_0 = -\frac{1}{2}S'/S + \sum_{k=1}^{n} -a_k I_k'/I_k$.

Case 1. $A_0 + A_1 \ge A_1 + A_2$

Then

$$\begin{aligned}\mu_2(M^{[2]}) &= -(2\delta + \nu_1) + \sum_{k=1}^{n} c\beta_k(p_k S - I_k) - \frac{1}{2}\frac{S'}{S} - 2\sum_{k=1}^{n} a_k \frac{I_k'}{I_k}\\ &= -(2\delta + \nu_1) + \sum_{k=1}^{n} c\beta_k p_k S - \frac{\delta}{2}\frac{S_0 - S}{S} - \frac{1}{2}\sum_{k=1}^{n} c\beta_k I_k\\ &\quad - 2\sum_{k=1}^{n} a_k p_k \sum_{j=1}^{n} c\beta_j \frac{I_j}{I_k} S + 2\sum_{k=1}^{n}(\delta + \nu_k)a_k.\end{aligned}$$

Since $U + V \ge 2\sqrt{UV}$ we get

$$\begin{aligned}\mu_2(M^{[2]}) &\le -(2\delta + \nu_1) + \sum_{k=1}^{n} c\beta_k p_k S - \frac{\delta}{2}\frac{S_0 - S}{S} - \frac{1}{2}\sum_{k=1}^{n} c\beta_k I_k\\ &\quad - 2\sum_{k,j=1}^{n} \sqrt{a_k a_j p_k p_j c\beta_k c\beta_j}\, S + 2\sum_{k=1}^{n}(\delta + \nu_k)a_k\\ &= -\frac{\delta}{2}\frac{S_0 - S}{S} - \frac{1}{2}\sum_{k=1}^{n} c\beta_k I_k + E + FS\\ &\le E + FS\end{aligned}$$

with $E = -(2\delta+\nu_1)+2\sum_{k=1}^{n}(\delta+\nu_k)a_k$ and $F = \sum_{k=1}^{n} c\beta_k p_k - 2\left(\sum_{k=1}^{n}\sqrt{a_k p_k c\beta_k}\right)^2$. Letting $a_k = b_k^2$ with $b_k > 0$, $k = 1,\ldots,n$, we see that $E = 0$ and $F = 0$ are, respectively, equivalent to

$$\sum_{k=1}^{n}(\delta+\nu_k)b_k^2 = \frac{1}{2}(2\delta+\nu_1)$$

$$\sum_{k=1}^{n}\sqrt{p_k c\beta_k}\, b_k = \sqrt{\frac{1}{2}\sum_{k=1}^{n} p_k c\beta_k}$$

which are, respectively, the equations of an ellipsoid and a hyperplane. In order to obtain $\mu_2(M^{[2]}) < -\epsilon$ for some $\epsilon > 0$, we want to choose b_k, $k = 1,\ldots,n$ such that $E, F < 0$. This is equivalent to finding a point which lies inside the ellipsoid $E = 0$ and above the hyperplane $F = 0$. This can be done only if the point on the ellipsoid whose tangent hyperplane is parallel to the given hyperplane, lies above the given hyperplane. Thus, we want to solve the equation $\nabla E = \alpha\nabla F$ for some $\alpha \in \mathbb{R}$. This gives

$$b_k = b_k^* = \frac{\alpha\sqrt{p_k c\beta_k}}{2(\delta+\nu_k)}.$$

Filling this into the equation of the ellipsoid $E = 0$ gives

$$\begin{aligned} 0 &= -(2\delta+\nu_1) + 2\sum_{k=1}^{n}(\delta+\nu_k)(b_k^*)^2 \\ &= -(2\delta+\nu_1) + 2\sum_{k=1}^{n}\frac{\alpha^2 p_k c\beta_k}{4(\delta+\nu_k)} \\ &= -(2\delta+\nu_1) + \frac{\alpha^2}{2}\frac{R_0}{S_0} \end{aligned}$$

So, $\alpha = \sqrt{2(2\delta + \nu_1)S_0/R_0}$. We can now evaluate F at this point, getting

$$\begin{aligned} F &= \sum_{k=1}^{n} p_k c\beta_k - 2\alpha^2 \Big(\sum_{k=1}^{n} \frac{p_k c\beta_k}{2(\delta + \nu_k)} \Big)^2 \\ &= \sum_{k=1}^{n} p_k c\beta_k - \frac{\alpha^2}{2} \Big(\frac{R_0}{S_0} \Big)^2 \\ &= \sum_{k=1}^{n} p_k c\beta_k - (2\delta + \nu_1) \frac{R_0}{S_0}. \end{aligned}$$

If $F(b_k^*) < 0$ then there are points inside the ellipsoid and above the hyperplane $F = 0$ and so, a_k, $k = 1, \ldots, n$ can be chosen to make $E, F < 0$. Note that $F(b_k^*) < 0$ can be rewritten as

$$\sum_{k=1}^{n} \frac{p_k c\beta_k (\delta + \nu_1 - \nu_k)}{\delta + \nu_k} > 0. \tag{6.7}$$

Thus, we can see that a sufficient condition for $\mu_2(M^{[2]}) < -\epsilon$ is that $\nu_k \leq \delta + \nu_1$ for $k = 1, \ldots, n$.

Case 2. $A_0 + A_1 < A_1 + A_2$

Then

$$\begin{aligned} \mu_2(M^{[2]}) &= -(2\delta + \nu_1 + \nu_2) - 2 \sum_{k=1}^{n} a_k p_k \sum_{j=1}^{n} c\beta_j \frac{I_j}{I_k} S + 2 \sum_{k=1}^{n} (\delta + \nu_k) a_k \\ &< E + FS \\ &\leq -\epsilon \end{aligned}$$

for some $\epsilon > 0$ if each a_k, $k = 1, \ldots, n$ is chosen in the same way as in Case 1.

In either case, if (6.7) is satisfied then we have

$$\mu_2(M^{[2]}) \leq -\epsilon < 0. \tag{6.8}$$

We now demonstrate the following global stability result.

Proposition 6.2. *Suppose (6.7) is satisfied. If $R_0 > 1$ then P_* is stable attracting all solutions except those which lie on the disease-free axis. If $R_0 \leq 1$ then P_0 is globally stable.*

Proof. Suppose $R_0 < 1$. Letting $D = \{(S, I_1, \ldots, I_n) : N \leq 2S_0\}$, we see that equation (6.2) implies that D is positively invariant. For $R_0 < 1$, the only equilibrium in D is P_0 which is locally asymptotically stable. At all points in the boundary of D, trajectories enter the interior, except for the disease-free axis where solutions go to P_0. Thus, the boundary of D contains no omega limit points except P_0. Since (6.8) holds on the interior of D, Theorem 3.11 implies that all solutions limit to P_0.

Suppose $R_0 > 1$. Again, the only omega limit point on the boundary of D is P_0 which repels the interior of D. Thus, int D contains a compact absorbing set which contains a single equilibrium P_*. By Theorem 3.6, P_* attracts all solutions in the interior of D. Since trajectories on the boundary of D which are not on the disease-free axis, move to the interior, we see that the result is proven. □

Remarks. (1) Since (6.7) is satisfied, when $\nu_k \leq \delta + \nu_1$ for all $k = 1, \ldots, n$, we can interpret (6.7) as a condition on how different the disease-related removal rates are for the various infective classes. fails.

(2) It is worth noting that although it is sufficient that (6.7) be satisfied in order to apply Proposition 6.2, it is not necessary. Numerical simulations have shown that there is a globally stable endemic equilibrium for $R_0 > 1$ even when (6.7)

6.5 Conclusions

Suppose $R_0 < 1$. Then if a small amount of the disease is introduced into the population, it will be unable to invade and will disappear without the occurrence

of an epidemic. If (6.7) is satisfied then the disease will die out of the population regardless of the starting conditions.

On the other hand, suppose $R_0 > 1$. Then a small amount of the disease will persist if introduced into the population. Furthermore, if (6.7) is satisfied, then the disease will go to a constant endemic level in the population. In fact, if (6.7) is satisfied, then once present, the disease will eventually go to the constant level given by P_* regardless of the starting conditions.

CHAPTER 7

A Model of Staged Progression and Amelioration

7.1 Introduction

Many compartment models for the spread of an infectious disease involve a single class for infectious individuals. While this is a practical assumption for diseases with short infectious periods, such as measles or influenza, it is not generally suitable for HIV/AIDS. For HIV/AIDS, the infectious period typically lasts anywhere from 5 to 15 years.

Models for the spread of HIV/AIDS often incorporate staged progression [27, 43] where an individual may advance through several infective stages before developing full-blown AIDS. Sometimes these stages are meant to correspond to T4 cell count ranges [43]. Typically, these models assume a monotone progression through the infective stages, so that there is no return once an individual has passed a certain stage of infection (or T4 cell count). With recent advances in drug therapies, it is necessary to modify this assumption and allow for amelioration, in which individuals may move from more advanced stages of infection to less advanced stages. Our efforts will concentrate on a model with three stages of infection.

In [27], Hyman et al. study a model of staged progression with proportional mixing and constant recruitment. In [43], Lin et al. study a model of staged progression with proportional mixing and recruitment which is proportional to the total population size is studied. Neither of these models includes amelioration. For each model, the reproduction ratio R_0 is calculated and it is shown that if $R_0 < 1$ then the only fixed point is the disease-free equilibrium which is locally asymptotically stable. If $R_0 > 1$ then the disease-free equilibrium is unstable and

there is a unique endemic equilibrium. In [43], it is shown for two infective stages that if $R_0 \leq 1$ then the disease-free equilibrium is globally stable and if $R_0 > 1$ then the endemic equilibrium attracts all solutions except for the disease-free equilibrium.

In this chapter, we present a model of staged progression which has three infective stages and allows for amelioration. This model may be appropriate for a jail or some other setting for which the total population remains fixed. As individuals are removed from the population, they are immediately replaced with new individuals in the susceptible class. This has the unusual attribute that an increase in disease related deaths results in an increase in the recruitment of susceptibles.

Using mass action for the force of infection, a threshold value S_* is found. If the total population is less than S_* then the disease dies out. If the total population is greater than S_* then the disease persists and there is a unique endemic equilibrium. Using the techniques described in Sections 3.3 and 3.4, it is shown that under a restriction on the parameters, the endemic equilibrium attracts all solutions except the disease-free equilibrium when the total population is greater than S_*.

In the next chapter a model of staged progression and amelioration is studied which uses proportional mixing and recruitment proportional to the total population. It is a generalization of the model found in [43].

7.2 Model Formulation

A population of size N is divided into a susceptible group of size S and infective groups I_1, I_2, I_3. Thus, $N = S + I_1 + I_2 + I_3$. The transfer diagram is as

follows.

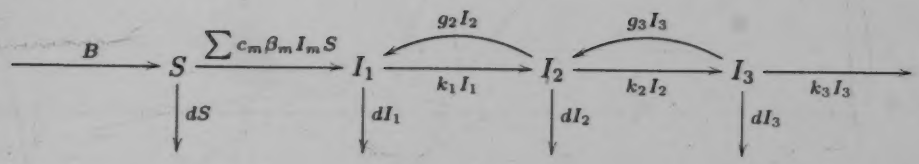

Figure 7.1: Transfer diagram for a model of staged progression.

The rate constant for removal not directly related to the disease is d. For $m = 1, 2$, the parameters k_m and g_{m+1} are the rate constants for movement from I_m to I_{m+1} and from I_{m+1} to I_m, respectively. The rate at which individuals in I_3 leave the population for disease related reasons is $k_3 I_3$. The average number of contacts made by a susceptible individual with individuals in infective class I_m per unit of time is $c_m I_m$. The probability that a contact between a susceptible and an infective in class I_m results in a new infection is β_m for $m = 1, 2, 3$. The number of new infections per unit time therefore, is $\sum_{m=1}^{3} c_m \beta_m I_m S$. The recruitment rate B of new individuals is chosen to keep the total population constant. Thus, $B = d(S + I_1 + I_2 + I_3) + k_3 I_3$. We assume that $c_m, \beta_m, k_m > 0$ for $m = 1, 2, 3$. All other parameters are assumed to be non-negative.

The differential equation for the active population subgroups is

$$\begin{aligned} S' &= d(I_1 + I_2 + I_3) - \sum_{m=1}^{3} c_m \beta_m I_m S + k_3 I_3 \\ I_1' &= \sum_{m=1}^{3} c_m \beta_m I_m S - (k_1 + d) I_1 + g_2 I_2 \\ I_2' &= k_1 I_1 - (k_2 + g_2 + d) I_2 + g_3 I_3 \\ I_3' &= k_2 I_2 - (k_3 + g_3 + d) I_3. \end{aligned} \tag{7.1}$$

We denote the vector field described in (7.1) by f. It can be verified that the non-negative cone $\mathbb{R}^4_{\geq 0}$ is positively invariant under (7.1). Biologically, this means that populations which start non-negative will remain so.

7.3 The Equilibria

Every point on the disease-free axis is an equilibrium. We label these by $P_0(N) = (N, 0, 0, 0)$. For every N, $P_*(N) = (S_*, I_{1*}, I_{2*}, I_{3*})$ is an equilibrium where

$$S_* = \frac{(k_1+d)\big[(k_2+g_2+d)(k_3+g_3+d) - k_2g_3\big] - k_1g_2(k_3+g_3+d)}{c_1\beta_1\big[(k_2+g_2+d)(k_3+g_3+d) - k_2g_3\big] + c_2\beta_2k_1(k_3+g_3+d) + c_3\beta_3k_1k_2}$$

$$I_{1*} = \frac{(k_2+g_2+d)(k_3+g_3+d) - k_2g_3}{(k_2+g_2+d)(k_3+g_3+d) - k_2g_3 + k_1(k_3+g_3+d) + k_1k_2}\Big(N - S_*\Big)$$

$$I_{2*} = \frac{k_1(k_3+g_3+d)}{(k_2+g_2+d)(k_3+g_3+d) - k_2g_3 + k_1(k_3+g_3+d) + k_1k_2}\Big(N - S_*\Big)$$

$$I_{3*} = \frac{k_1k_2}{(k_2+g_2+d)(k_3+g_3+d) - k_2g_3 + k_1(k_3+g_3+d) + k_1k_2}\Big(N - S_*\Big).$$

Note that S_* is independent of N. These equilibria are only in the positive orthant if $N \geq S_*$. If $N = S_*$ then P_* coincides with P_0.

Since $N' = 0$, the total population is constant. This means that N is a first integral. Of interest to us is the fact that for a fixed $N = N_0$, the three dimensional manifold $\Gamma = \{V := S + I_1 + I_2 + I_3 - N_0 = 0,\ S, I_1, I_2, I_3 \geq 0\}$ is positively invariant under the flow described by (7.1). We will study the stability of the equilibria relative to the invariant manifold in which they lie.

Let $h = -[c_1\beta_1, c_2\beta_2, c_3\beta_3]^T$ and

$$L = \begin{bmatrix} -(k_1+d) & k_1 & 0 \\ g_2 & -(k_2+g_2+d) & k_2 \\ 0 & g_3 & -(k_3+g_3+d) \end{bmatrix}.$$

If $a = [a_1, a_2, a_3]^T$ is defined by the equation $La = h$, then it can be shown that each a_m is positive and that $W = a_1I_1 + a_2I_2 + a_3I_3$ is a Lyapunov function satisfying

$W' = (\frac{S}{S_*} - 1)\sum_{m=1}^{3} c_m\beta_m I_m$. Thus, if $N \leq S_*$ then W is decreasing in $\Gamma \setminus P_0$ and so P_0 is globally stable in Γ. On the otherhand, if $N > S_*$ then W is increasing near P_0 and so P_0 is repelling. A similar calculation is done in greater detail in Section 8.3.

7.4 Global Stability for $N > S_*$

For the purpose of the following calculations, we make the simplifying assumption that $g_2 = g_3 = g$ and $k_j = k$, $c_j\beta_j = c\beta$ for $j = 1, 2, 3$.

Consider the new system

$$x' = H(x) := f(x) + VE(x) \tag{7.2}$$

where $E = [c\beta S - d, -c\beta N, 0, 0]^T$. Then on Γ, equations (7.1) and (7.2) describe the same dynamics. The associated Jacobians, however, are different. On Γ, the Jacobian of (7.2) is given by

$$\begin{aligned}\frac{\partial H}{\partial x} &= \frac{\partial f}{\partial x} + V\frac{\partial E}{\partial x} + \nabla VE \\ &= \frac{\partial f}{\partial x} + \nabla VE \\ &= \frac{\partial f}{\partial x} + [1,1,1,1]\begin{bmatrix} c\beta S - d \\ -c\beta N \\ 0 \\ 0 \end{bmatrix}.\end{aligned}$$

Calculating $\frac{\partial f}{\partial x}$ and using the relationship $N = S + I_1 + I_2 + I_3$ yields

$$\frac{\partial H}{\partial x} = \begin{bmatrix} c\beta(2S-N) - d & 0 & 0 & k \\ -c\beta S & c\beta(S-N) - (k+d) & g + c\beta(S-N) & c\beta(S-N) \\ 0 & k & -(k+g+d) & g \\ 0 & 0 & k & -(k+g+d) \end{bmatrix}. \tag{7.3}$$

Following (3.13) and (3.14) we get $\nu(x) = E_1 + E_2 + E_3 + E_4 = c\beta(S-N) - d$. Let $M = Q_f Q^{-1} + Q\frac{\partial H}{\partial x}^{[3]}Q^{-1} - \nu I_{4\times 4}$ where $Q = I_1^{-1}I_{4\times 4}$, $\frac{\partial H}{\partial x}^{[3]}$ is the third additive

compound of $\frac{\partial H}{\partial x}$ [see Appendix A] and $I_{4\times 4}$ is the four by four identity matrix. Then

$$M = \operatorname{diag}\begin{pmatrix} c\beta(2S-N)-(2k+g+2d)-\frac{I_1'}{I_1} \\ c\beta(2S-N)-(2k+g+2d)-\frac{I_1'}{I_1} \\ c\beta S-(2k+2g+2d)-\frac{I_1'}{I_1} \\ -(3k+2g+2d)-\frac{I_1'}{I_1} \end{pmatrix} + \begin{bmatrix} 0 & g & c\beta(N-S) & k \\ k & 0 & g+c\beta(S-N) & 0 \\ 0 & k & 0 & 0 \\ 0 & 0 & -c\beta S & 0 \end{bmatrix}$$

$$= \operatorname{diag}\begin{pmatrix} c\beta(S-N)-(k+g+d)-\Phi \\ c\beta(S-N)-(k+g+d)-\Phi \\ -(k+2g+d)-\Phi \\ -c\beta S-(2k+2g+d)-\Phi \end{pmatrix} + \begin{bmatrix} 0 & g & c\beta(N-S) & k \\ k & 0 & g+c\beta(S-N) & 0 \\ 0 & k & 0 & 0 \\ 0 & 0 & -c\beta S & 0 \end{bmatrix}$$

where $\Phi = (c\beta S(I_2+I_3)+gI_2)/I_1 > 0$. Using the Lozinskii measure μ_1 corresponding to the l_1 norm [see Table 2.1], we find that $\mu_1(Q) = -(d+\Phi) < 0$.

If $N > S_*$, then the system persists. Thus, there is a compact set in the interior of Γ which is absorbing in $\Gamma \setminus P_0$. Therefore, by Theorem 3.14, P_* is globally stable in $\Gamma \setminus P_0$ for $N > S_*$.

7.5 Conclusions

If $N \leq S_*$ then the disease-free equilibrium is globally attracting and the disease dies out.

If $N > S_*$ then the disease persists in the populations and there is a unique endemic equilibrium. If $g_2 = g_3$, $k_1 = k_2 = k_3$, and $c_1\beta_1 = c_2\beta_2 = c_3\beta_3$, and the disease is present, then the disease will eventually go to the endemic equilibrium levels.

CHAPTER 8

A Model of HIV/AIDS with Staged Progression and Amelioration

8.1 Introduction

We now present another model of staged progression and amelioration. In this model, the incidence is determined by using proportional mixing and the recruitment of new individuals is proportional to the total active population. This is a generalization of the model studied by Lin et al. in [43]. A discussion of staged progression can be found in Section 7.1.

Treatment increases the expected available time for the transmission of HIV. We examine the impact that this has on the long-term dynamics of the disease. It is shown that it is possible that treatment may result in the disease persisting in the population or in the disease dying out, depending on parameter values.

In Section 8.2, a model is presented which allows for infectives to undergo amelioration, moving from more advanced stages of infection (low T4 cell counts) to less advanced stages of infection (high T4 cell counts). Equations are given that describe the evolution of the proportions of the active population which lie in each compartment.

In Section 8.3, a threshold quantity is found in terms of the model parameters. Below this threshold, the disease-free equilibrium is locally stable. Above the threshold, the system is uniformly persistent. In Section 8.4, results are given for the case where the active population involves two infective stages. In Section 8.5, the model is studied with three infective stages. Under a restriction on the parameters, the uniqueness of the endemic equilibrium is demonstrated. This is done using a new technique in Section 8.5.1. In Section 8.5.2, the global stability is resolved

for the case when treatment is sufficiently effective, using the techniques discussed in Sections 3.3 and 3.4. In Section 8.6, the dynamics of the total population sizes are studied.

8.2 Model Formulation

A population is divided into a susceptible group of size S, infective groups $I_1, I_2, \ldots, I_r$, and a group of size A which is removed from the active population. Thus, the total active population is $N = S + I_1 + \cdots + I_r$. The transfer diagram is as follows.

Figure 8.1: Transfer diagram for a model of staged progression.

The rate at which new individuals enter the population being studied, all entering into the susceptible class, is bN. The rate at which deaths not directly related to the disease occur is dN. We assume that d is non-negative and allow that it may be a function of the state variables. For $m = 1, \ldots, r-1$, k_m and g_{m+1} are the rate constants for movement from I_m to I_{m+1} and from I_{m+1} to I_m, respectively. The rate at which individuals in I_r move to A is $k_r I_r$. At this point the infective has succumbed to secondary diseases which will result in death. It is assumed that individuals in class A are too sick to be actively spreading the disease and so, they are removed from the population. The average number of contacts made by a susceptible individual per unit of time is c. For $m = 1, \ldots, r$, β_m is the probability that a contact between a susceptible and an infective in class I_m results

in a new infection. Using proportional mixing, the incidence is therefore given by $\sum_{m=1}^{r} c\beta_m \frac{I_m}{N} S$. We assume that $b, c > 0$ and $\beta_m, k_m > 0$ for $m = 1, \ldots, r$. All other parameters are assumed to be non-negative.

If $g_m = 0$ for $m = 2, \ldots, r$, then this model reduces to the model studied in [43]. For notational convenience, we will sometimes refer to g_1 in which case, it is assumed that $g_1 = 0$.

The differential equation for the active population subgroups is

$$\begin{aligned} S' &= bN - dS - \sum_{m=1}^{r} c\beta_m \frac{I_m}{N} S \\ I_1' &= \sum_{m=1}^{r} c\beta_m \frac{I_m}{N} S - (k_1 + d)I_1 + g_2 I_2 \\ I_m' &= k_{m-1} I_{m-1} - (k_m + g_m + d)I_m + g_{m+1} I_{m+1} \qquad \text{for } m = 2, \ldots, r-1 \\ I_r' &= k_{r-1} I_{r-1} - (k_r + g_r + d)I_r. \end{aligned} \tag{8.1}$$

It can be verified that the non-negative cone $\mathbb{R}^{r+1}_{\geq 0}$ is positively invariant under (8.1). We note that it is biologically meaningful that subpopulations which start non-negative will remain so.

Let $X = [S, I_1, \ldots, I_r]^T$. Then (8.1) can be written as $X' = H(X) - dX$ where

$$H(X) = \begin{bmatrix} bN - \sum_{m=1}^{r} c\beta_m \frac{I_m}{N} S \\ \sum_{m=1}^{r} c\beta_m \frac{I_m}{N} S - k_1 I_1 + g_2 I_2 \\ \vdots \\ k_{r-1} I_{r-1} - (k_r + g_r) I_r \end{bmatrix}$$

is homogeneous of degree 1 and dX points in the radial direction. Thus, this (r+1)-dimensional system can be projected onto the r-dimensional hyperplane

$$\tilde{\Gamma}_r = \{(s, i_1, \ldots, i_r) : V = s + i_1 + \cdots + i_r - 1 = 0\}$$

where $s = \frac{S}{N}$ and $i_m = \frac{I_m}{N}$ for $m = 1, \ldots, r$ are the fractions of the active population

which are in the respective groups. This yields the equation

$$
\begin{aligned}
s' &= b(1-s) - \sum_{m=1}^{r} c\beta_m i_m s + k_r i_r s \\
i_1' &= \sum_{m=1}^{r} c\beta_m i_m s - (k_1+b)i_1 + g_2 i_2 + k_r i_r i_1 \\
i_m' &= k_{m-1} i_{m-1} - (k_m + g_m + b)i_m + g_{m+1} i_{m+1} + k_r i_r i_m \qquad \text{for } m = 2, \ldots, r-1 \\
i_r' &= k_{r-1} i_{r-1} - (k_r + g_r + b)i_r + k_r i_r^2.
\end{aligned}
\tag{8.2}
$$

Let $\Gamma_r = \tilde{\Gamma}_r \cap \mathbb{R}^{r+1}_{\geq 0}$. We think of (8.2) as being defined on $\mathbb{R}^{r+1}_{\geq 0}$ and having Γ_r as a positively invariant manifold. The point $P_0 = (1, 0, \ldots, 0)$ is the disease-free equilibrium of (8.2). In fact, P_0 is the only equilibrium on the boundary of $\mathbb{R}^{r+1}_{\geq 0}$, so at an endemic equilibrium, $i_m > 0$ for all $m = 1, \ldots, r$.

8.3 The Disease-Free Equilibrium and Its Local Stability

We construct a Lyapunov function in order to determine the local stability of the disease-free equilibrium. Consider the tri-diagonal matrix

$$
L = \begin{bmatrix}
-(k_1+b) & k_1 & & & & \\
g_2 & -(k_2+g_2+b) & k_2 & & & \\
 & \ddots & \ddots & \ddots & & \\
 & & g_{r-1} & -(k_{r-1}+g_{r-1}+b) & k_{r-1} & \\
 & & & g_r & -(k_r+g_r+b)
\end{bmatrix}.
$$

Since L is diagonally dominant in rows, L^{-1} exists. Let $h = -[c\beta_1, \ldots, c\beta_r]^T$ and $a = [a_1, \ldots, a_r]^T$ with $a = L^{-1}h$. Note that by using the relationship $La = h$ and the form of L, it can be shown that $a_m > 0$ for $m = 1, \ldots, r$.

Let $W = \sum_{m=1}^{r} a_m i_m$. Then by (8.2),

$$
W' = (\sigma s - 1) \sum_{m=1}^{r} c\beta_m i_m + k_r i_r W \tag{8.3}
$$

where $\sigma = a_1$. Since $La = h$, we can use Cramer's Rule to express σ as

$$\sigma = \frac{\det \tilde{L}}{\det L} \tag{8.4}$$

where

$$\tilde{L} = \begin{bmatrix} -c\beta_1 & k_1 & & & \\ -c\beta_2 & -(k_2+g_2+b) & k_2 & & \\ -c\beta_3 & g_3 & -(k_3+g_3+b) & \ddots & \\ \vdots & & \ddots & \ddots & k_{r-1} \\ -c\beta_r & & & g_r & -(k_r+g_r+b) \end{bmatrix}.$$

The stability of the disease-free equilibrium is determined by whether or not σ is greater than 1.

Theorem 8.1. *If $\sigma < 1$ then P_0 is locally asymptotically stable in Γ_r under the flow given by (8.2). If $\sigma > 1$ then P_0 is unstable and (8.2) is uniformly persistent in Γ_r.*

Proof. Note that there exists a positive constant C such that $CW \leq \sum_{m=1}^{r} c\beta_m i_m$ for $i_m \geq 0$, $m = 1, \ldots, r$. By (8.3), if $\sigma < 1$, then in a sufficiently small neighbourhood of P_0, $W' \leq \frac{C}{2}(\sigma - 1)W$. Thus, W goes to zero exponentially. Therefore each i_m goes to zero exponentially and so P_0 is locally asymptotically stable. Similarly, if $\sigma > 1$, then in a neighbourhood of P_0, we have $W' \geq \frac{C}{2}(\sigma - 1)W$ and so W increases and P_0 is unstable. In this case, at all points on the boundary of Γ_r except P_0, solutions flow to the interior of Γ_r, and near P_0 there are level surfaces of W which the flow crosses, moving away from P_0. Thus, (8.2) is uniformly persistent in Γ_r if $\sigma > 1$. □

Corollary 8.2. *An endemic equilibrium exists when $\sigma > 1$.*

Proof. We construct a ball shaped set Δ on which the flow is positively invariant. Let $\Delta = \Gamma_r \setminus \{W < \epsilon\}$ for some $\epsilon > 0$. The set Δ can be thought of as Γ_r with a

neighbourhood of P_0 cut out. By (8.3), if $\sigma > 1$ and ϵ is sufficiently close to zero then solutions cross $\{W = \epsilon\}$ from the outside of Δ to the inside. Combining this with the positive invariance of Γ_r, we see that Δ is positively invariant.

Thus it follows from Brouwer's Fixed Point Theorem [17] that Δ contains an equilibrium. Since the only equilibrium on the boundary of Γ_r is $P_0 \notin \Delta$, we see that Γ_r must contain an endemic equilibrium. □

Remarks. (1) If $g_m = 0$ and $k_m = k$ then (8.4) gives $\sigma = \sum_{m=1}^{r} (\frac{k}{k+b})^{m-1} \frac{c\beta_m}{k+b}$, which agrees with the threshold found in [43].

(2) Theorem 8.1 establishes σ as a sharp threshold. If $\sigma < 1$ then the disease-free equilibrium is stable and, locally, the disease dies out. If $\sigma > 1$ then the disease persists and becomes endemic.

(3) It can be shown that if J is the variational matrix for (8.2) evaluated at P_0, then $\det(J)$ is zero if and only if $\sigma = 1$. Thus, P_0 is an isolated equilibrium for $\sigma \neq 1$.

Interpretation of σ for $r = 2$ and $r = 3$.

Consider a newly infected individual in a population which is otherwise, completely susceptible. The threshold parameter should be equal to the expected number of new infections caused by this individual [13, 54]. For a general r, we expect σ to be in the form

$$\sigma = \sum_{m=1}^{r} c\beta_m \frac{1}{k_m + g_m + b} Q_m$$

where $\frac{1}{k_m+g_m+b}$ can be thought of as the expected waiting time in class i_m per visit and Q_m is the expected number of times that an infective will enter class i_m.

By (8.4), when $r = 2$ we get

$$\sigma = \frac{c\beta_1}{k_1 + b} \frac{1}{1 - q_{12}} + \frac{c\beta_2}{k_2 + g_2 + b} \frac{k_1}{k_1 + b} \frac{1}{1 - q_{12}}$$

where $q_{12} = \frac{k_1}{(k_1+b)} \frac{g_2}{(k_2+g_2+b)}$ is the probability of moving from one of i_1 and i_2 to the other and back again. The fraction $\frac{1}{1-q_{12}}$ gives the expected number of round trips between i_1 and i_2. The term $\frac{k_1}{k_1+b}$ is the probability of advancing from i_1 to i_2. So, $Q_1 = \frac{1}{1-q_{12}}$ and $Q_2 = \frac{k_1}{k_1+b} \frac{1}{1-q_{12}}$.

For $r = 3$, (8.4) implies

$$\sigma = \frac{c\beta_1}{k_1+b} \frac{1-q_{23}}{1-(q_{12}+q_{23})} + \frac{c\beta_2}{k_2+g_2+b} \frac{k_1}{k_1+b} \frac{1}{1-(q_{12}+q_{23})} + \frac{c\beta_3}{k_3+g_3+b} \frac{k_1}{k_1+b} \frac{k_2}{k_2+g_2+b} \frac{1}{1-(q_{12}+q_{23})} \tag{8.5}$$

where $q_{23} = \frac{k_2}{(k_2+g_2+b)} \frac{g_3}{(k_3+g_3+b)}$ is the probability of moving from one of i_2 and i_3 to the other and directly back again. Although algebraically more complicated, the following expression may make the interpretation of Q_1 and Q_3 more clear.

$$\sigma = \frac{c\beta_1}{k_1+b} \frac{1}{1-q_{12}\frac{1}{1-q_{23}}} + \frac{c\beta_2}{k_2+g_2+b} \frac{k_1}{k_1+b} \frac{1}{1-(q_{12}+q_{23})} + \frac{c\beta_3}{k_3+g_3+b} \frac{k_1}{k_1+b} \frac{1}{1-q_{12}} \frac{k_2}{k_2+g_2+b} \frac{1}{1-q_{23}\frac{1}{1-q_{12}}}$$

We describe the second term in the right-hand side of (8.5). Each time that an infective enters class i_2, the expected number of new infections is $\frac{c\beta_2}{k_2+g_2+b}$ since $\frac{1}{k_2+g_2+b}$ is the average waiting time. The fraction $\frac{k_1}{k_1+b}$ is the probability that the individual advances from i_1 to i_2 after first being infected. Since $q_{12}+q_{23}$ represents the probability that someone in i_2 leaves this class and returns, $\frac{1}{1-(q_{12}+q_{23})} = 1 + (q_{12}+q_{23}) + (q_{12}+q_{23})^2 + \ldots$ is the expected number of visits to i_2 given that an individual has advanced to i_2. Thus, $Q_2 = \frac{k_1}{k_1+b} \frac{1}{1-(q_{12}+q_{23})}$. Similar explanations can be found for the other terms.

8.4 Two Infective Stages

When $r = 2$, (8.2) becomes

$$\begin{aligned} s' &= b(1-s) - (c\beta_1 i_1 s + c\beta_2 i_2 s) + k_2 i_2 s \\ i_1' &= (c\beta_1 i_1 s + c\beta_2 i_2 s) - (k_1 + b)i_1 + g_2 i_2 + k_2 i_2 i_1 \\ i_2' &= k_1 i_1 - (k_2 + g_2 + b)i_2 + k_2 i_2^2. \end{aligned} \tag{8.6}$$

The following result can be proven using Corollary 3.21, as was done for Theorem 4.1 of [43] which involves the analogous result for the case when $g_2 = 0$.

Theorem 8.3. *Every omega limit point of (8.6) is an equilibrium.*

If we make the assumption that $k_1 = k_2$ and $\beta_1 = \beta_2$, then we can show that for $\sigma \leq 1$ there is no endemic equilibrium and that if $\sigma > 1$, then there is a unique endemic equilibrium. This is proven in the same manner as Theorem 8.6. Combining this with Theorem 8.1, we can state the following result.

Theorem 8.4. *Suppose $k_1 = k_2$ and $\beta_1 = \beta_2$. If $\sigma \leq 1$ then the equilibrium $P_0 = (1, 0, 0)$ is globally stable in Γ_2. If $\sigma > 1$, then there is a unique endemic equilibrium which is globally asymptotically stable in $\Gamma_2 \setminus P_0$.*

8.5 Three Infective Stages

Let $r = 3$. Throughout Sections 8.5.1 and 8.5.2, we assume, for algebraic convenience, that $k_m = k$ and $\beta_m = \beta$ for $m = 1, 2, 3$ and that $g_m = g$ for $m = 2, 3$. It should be noted that although this assumption is quite restrictive, it does not reduce the model to being equivalent to a model with one infectious stage, because the dynamics of a cohort of individuals infected at the same instant differs between

the models. This can be seen by looking at how the size of the cohort varies over time.

8.5.1 Uniqueness of the Endemic Equilibrium

Let f be the vector field described by the right-hand side of (8.2). Since Γ_3 is positively invariant, we can replace f with $F_1 = f + VE_1$ where $E_1 = [c\beta s, -c\beta s, 0, 0]^T$. This, gives the differential equation

$$\begin{aligned} s' &= b(1-s) - c\beta(1-s)s + ki_3 s \\ i_1' &= c\beta(1-s)s - (k+b)i_1 + gi_2 + ki_3 i_1 \\ i_2' &= ki_1 - (k+g+b)i_2 + gi_3 + ki_3 i_2 \\ i_3' &= ki_2 - (k+g+b)i_3 + ki_3^2. \end{aligned} \tag{8.7}$$

Working with this new system, equations (3.13) and (3.14) give $\nu_1(x) := \nu = ki_3 - b$.

Let B be the variational matrix for (8.7). Then

$$B = \begin{bmatrix} ki_3 - b + c\beta(2s-1) & 0 & 0 & ks \\ c\beta(1-2s) & ki_3 - b - k & g & ki_1 \\ 0 & k & ki_3 - b - k - g & ki_2 + g \\ 0 & 0 & k & 2ki_3 - b - k - g \end{bmatrix}.$$

Notice that on Γ_3 we have $[1,1,1,1]B = \nu_1(x)[1,1,1,1]$ and so $\nu_1(x)$ is an eigenvalue of B. Let $\nu_1(x)$, λ_1, λ_2 and λ_3 be the eigenvalues of B at an endemic equilibrium P_*. Then $\nu_1(x)$ describes the behavior which is normal to Γ_3 and the behavior near P_* in Γ_3 is determined by λ_1, λ_2 and λ_3.

It should be noted that because (8.2) and (8.7) are equal on Γ_3, that λ_1, λ_2 and λ_3 determine the behavior near P_* in Γ_3 not only with respect to (8.7), but also with respect to (8.2).

Since Γ_3 is positively invariant under the flow described by (8.7), we see that the restriction $F_1|_{\Gamma_3}$ is a mapping from Γ_3 to its tangent space $T\Gamma_3$. Note that Γ_3 and $T\Gamma_3$ are three dimensional manifolds. We will show that at an endemic equilibrium, the linearization of $F_1|_{\Gamma_3}$ is non-singular.

Lemma 8.5. *At an endemic equilibrium of (8.2),* $\lambda_1\lambda_2\lambda_3 < 0$.

Proof. Adding each of the other rows of B to the second row, we see that

$$\det(B) = \det\begin{bmatrix} \nu_1 + c\beta(2s-1) & 0 & 0 & ks \\ \nu_1 & \nu_1 & \nu_1 & \nu_1 \\ 0 & k & \nu_1 - (k+g) & ki_2 + g \\ 0 & 0 & k & \nu_1 + ki_3 - (k+g) \end{bmatrix}$$

$$= \nu_1\Big[-k^3 s + \big(\nu_1 + c\beta(2s-1)\big)\big[\big(\nu_1 - (k+g)\big)\big(\nu_1 + ki_3 - (k+g)\big) + k^2 - k(ki_2+g) - k\big(\nu_1 + ki_3 - (k+g)\big)\big]\Big]. \tag{8.8}$$

Note that $\frac{i_3'}{i_3} = 0$ implies $\nu_1 - (k+g) = -k\frac{i_2}{i_3}$ and that $\frac{i_2'}{i_3} = 0$ and $\frac{i_2}{i_3^2}i_3' = 0$ imply that $ki_2 + g = k(\frac{i_2}{i_3})^2 + ki_2 - k\frac{i_1}{i_3}$. Thus, we can rewrite (8.8) as

$$\det(B) = k^2\nu_1\Big[-ks + \big(\nu_1 + c\beta(2s-1)\big)\frac{1}{i_3}\big[i_1 + i_2(1-i_3) + i_3(1-i_2-i_3)\big]\Big]. \tag{8.9}$$

We observe that at an endemic equilibrium, $i_1 + i_2(1-i_3) + i_3(1-i_2-i_3) < i_1 + i_2 + i_3 = 1 - s$. Also, using $\frac{s'}{s} = 0$ and $\frac{s'}{1-s} = 0$, we get $\nu_1 + c\beta(2s-1) = c\beta s - \frac{b}{s} \le c\beta s - b = \frac{ki_3 s}{1-s}$. Writing the determinant of B as the product of its eigenvalues and canceling ν_1 from each side, (8.9) becomes

$$\lambda_1\lambda_2\lambda_3 < k^2\Big[-ks + \frac{ki_3 s}{1-s}\frac{1}{i_3}(1-s)\Big]$$
$$= 0.$$

□

Theorem 8.6. *If* $\sigma \le 1$ *then* P_0 *is the only equilibrium in* Γ_3. *If* $\sigma > 1$ *then there is a unique endemic equilibrium.*

Proof. By Lemma 8.5, for any $k_0 = (k, g, b, c\beta)$, the linearization of $F_1|_{\Gamma_3} : \Gamma_3 \to T\Gamma_3$ is non-singular at any endemic equilibrium x_0. Therefore, by the Implicit Function Theorem [17], there exist open sets $\mathcal{K} \ni k_0$, $\mathcal{X} \ni x_0$ such that for each $k \in \mathcal{K}$, there is a unique $x(k) \in \mathcal{X}$ such that $F_1(x(k); k) = 0$. Furthermore, the

mapping $k \mapsto x(k)$ is C^∞. We extend $\mathcal{K}$ to be the largest set of k values for which $x(k) \in \text{int}(\Gamma_3)$ can be defined and we note that $\mathcal{K}$ is open.

We now concern ourselves with the behavior on $\partial\mathcal{K}$, the boundary of $\mathcal{K}$. Let $\tilde{k} \in \partial\mathcal{K}$. Let $\{k_m\}$ be a sequence in $\mathcal{K}$ that converges to $\tilde{k}$ and let $\tilde{x} = \lim_{m\to\infty} x(k_m)$. Then

$$\begin{aligned} F_1(\tilde{x};\tilde{k}) &= F_1\Big(\lim_{m\to\infty} x(k_m); \lim_{m\to\infty} k_m\Big) \\ &= \lim_{m\to\infty} F_1\Big(x(k_m); k_m\Big) \\ &= 0 \end{aligned}$$

so $\tilde{x}$ is an equilibrium. If $\tilde{x}$ is an endemic equilibrium then $\lambda_1\lambda_2\lambda_3 < 0$ and so $\tilde{k}$ is an interior point of $\mathcal{K}$ which is a contradiction.

Thus, $\tilde{x}$ is a boundary equilibrium and so $\tilde{x} = P_0$ since P_0 is the only equilibrium on the boundary of Γ_3. Since $\{x(k_m)\}$ converges to P_0, we must have $\sigma(\tilde{k}) = 1$ because P_0 is isolated for $\sigma \neq 1$.

So, the only appearance or disappearance of equilibria that can happen is that equilibria may pass through P_0 when $\sigma = 1$.

In [43], it is shown that for $g = 0$, there is a unique endemic equilibrium if $\sigma > 1$ and there is no endemic equilibrium for $\sigma \leq 1$. We now show that the same is true for $g > 0$.

From (8.5) we have

$$\sigma = c\beta \frac{3k^2 + 2kg + 3kb + g^2 + 2gb + b^2}{k^3 + b(3k^2 + 2kg + 3kb + g^2 + 2gb + b^2)}$$

and we can check that $\frac{\partial\sigma}{\partial g} > 0$. Suppose we want to determine the number of endemic equilibria at $k_0 = (k, g, b, c\beta)$. Let $\bar{k} = (k, 0, b, c\beta(k_0))$ where $c\beta(k_0)$ is chosen so that $\sigma(\bar{k}) = \sigma(k_0)$. Note that $\bar{k}$ exists since σ is linear in $c\beta$. In fact, there is a path through the parameter space from $\bar{k}$ to k_0 such that σ, k and b

are constant along the path. For $\sigma \neq 1$, this means that the number of endemic equilibria at k_0 is the same as the number of endemic equilibria at $\bar{k}$ since change in the number of endemic equilibria is only possible when $\sigma = 1$.

Thus, for $\sigma > 1$ there is exactly one endemic equilibrium and for $\sigma < 1$ there are no endemic equilibria. By continuity, any endemic equilibria that exist for $\sigma = 1$ would necessarily still exist for some parameter values which give $\sigma < 1$. Thus, there can be no endemic equilibria when $\sigma = 1$ either. □

Remark. This proof can also be done using index theory, found in [25] for example.

8.5.2 Global Stability for $k \leq g + b$

First, observe that on Γ_3,

$$s' = (b - c\beta s)(1 - s) + ki_3 s. \tag{8.10}$$

Thus, if $b \geq c\beta$, then $s' > 0$ for all $s \in [0, 1)$ and so s increases to 1. In this case, solutions go to P_0 and it can be shown that $\sigma < 1$. From here on, we will assume that $b < c\beta$. In this case, if $s < \frac{b}{c\beta}$ then s' is positive and s will increase so that s is at least as large as $\frac{b}{c\beta}$. Thus, we only need to consider the subset of Γ_3 for which $c\beta s \geq b$.

Theorem 8.7. *For $r = 3$, if $k \leq g + b$ then there exists $\epsilon > 0$, Q, E and a Lozinskii measure μ such that $\mu(M) < -\epsilon$ on int(Γ_3), where M is given by equation (3.26).*

Proof. In studying the dynamics of (8.2) on Γ_3, we can replace f with $F_2 = f + VE_2$

where $E_2 = [c\beta s - ks, -ki_1, 0, 0]^T$. This gives the new equation is

$$\begin{aligned} s' &= b(1-s) - \sum_{m=1}^{3} c\beta i_m s + ki_3 s + V(c\beta s - ks) \\ i_1' &= \sum_{m=1}^{3} c\beta i_m s - (k+b)i_1 + gi_2 + ki_3 i_1 - Vki_1 \\ i_2' &= ki_1 - (k+g+b)i_2 + gi_3 + ki_3 i_2 \\ i_3' &= ki_2 - (k+g+b)i_3 + ki_3^2. \end{aligned} \tag{8.11}$$

Note that on Γ_3, (8.2) and (8.11) agree, but the associated Jacobians differ.

Following (3.13) and (3.14) we get $\nu_2(x) := \nu = k(i_3 - s - i_1) + c\beta s - b$ and the Jacobian matrix J is given by

$$\begin{bmatrix} c\beta(2s-1) + ki_3 - ks - b & -ks & -ks & 0 \\ c\beta(1-s) - ki_1 & c\beta s - (k+b) + ki_3 - ki_1 & c\beta s + g - ki_1 & c\beta s \\ 0 & k & ki_3 - (k+g+b) & g + ki_2 \\ 0 & 0 & k & 2ki_3 - (k+g+b) \end{bmatrix}.$$

Let $\tilde{M} = \tilde{Q}_f \tilde{Q}^{-1} + \tilde{Q} J^{[3]} \tilde{Q}^{-1} - \nu_2 I$ where $\tilde{Q} = \operatorname{diag}(1, 1, \frac{i_1}{i_2}, \frac{i_1}{i_2})$ and $J^{[3]}$ is the third additive compound of J [see Appendix A]. Then

$$\tilde{M} = \operatorname{diag} \begin{pmatrix} c\beta(2s-1) + 2ki_3 - (2k+g+2b) \\ c\beta(2s-1) + 3ki_3 - (2k+g+2b) \\ c\beta(s-1) + 3ki_3 + ki_1 - (2k+2g+2b) + \frac{i_1'}{i_1} - \frac{i_2'}{i_2} \\ 3ki_3 + ks - (3k+2g+2b) + \frac{i_1'}{i_1} - \frac{i_2'}{i_2} \end{pmatrix}$$

$$+ \begin{bmatrix} 0 & g + ki_2 & -c\beta s \frac{i_2}{i_1} & 0 \\ k & 0 & (c\beta s + g - ki_1)\frac{i_2}{i_1} & ks\frac{i_2}{i_1} \\ 0 & k\frac{i_1}{i_2} & 0 & -ks \\ 0 & 0 & c\beta(1-s) - ki_1 & 0 \end{bmatrix}.$$

Consider the linear system $\frac{du}{dt} = \tilde{M}u$ where $u = (u_1, u_2, u_3, u_4)^T$. Let $U = \max(|u_1|, |u_2|, |u_3| + |u_4|)$. By Proposition 2.1, U is a norm. We now claim that

$$D_+ U \le \left[\frac{i_1'}{i_1} + \xi \frac{s'}{s} - \epsilon\right] U \tag{8.12}$$

where D_+U is the right-hand time derivative of U [45], ξ is either 1 or 0, and $\epsilon > 0$. A proof of this claim can be found in Appendix C. Thus, by equation (2.2), at any point in $\text{int}(\Gamma_3)$, $\mu(\tilde{M}) \leq \frac{i_1'}{i_1} + \xi\frac{s'}{s} - \epsilon$, where μ is the Lozinskii measure associated with the norm U.

Let $Q = \frac{1}{i_1 s^\xi}\tilde{Q}$ and let $M = Q_f Q^{-1} + QJ^{[3]}Q^{-1} - \nu_2 I$. Then $M = -\left(\frac{i_1'}{i_1} + \xi\frac{s'}{s}\right)I + \tilde{M}$. Thus, by Proposition 2.2, $\mu(M) \leq -\epsilon$. □

Theorem 8.8. *Suppose $r = 3$ and $k \leq g + b$. If $\sigma > 1$ then P_* is globally asymptotically stable in $\Gamma_3 \setminus P_0$.*

Proof. By Theorem 8.1, the system is uniformly persistent and so there is a compact set K in the interior of Γ_3 which is absorbing on $\Gamma \setminus P_0$. By Theorem 8.6, P_* is the only equilibrium in $\Gamma_3 \setminus P_0$. By Theorem 8.7, $q_3(f, Q, E) < 0$ and so Theorem 3.18 implies P_* is globally asymptotically stable in $\Gamma_3 \setminus P_0$. □

Remarks. (1) The biological interpretation of the condition $k \leq g + b$ is that the combination of the availability and effictiveness of the medicine (measured by g) and the recruitment of new individuals into the population (measured by b), is sufficiently large compared to the rate at which infected individuals progress through the infective stages (given by k).

(2) Although $k \leq g + b$ is sufficient to conclude that the endemic equilibrium is globally stable for $\sigma > 1$, numerical evidence indicates that it is not a necessary condition.

8.5.3 General Parameters

Considering general parameters for $r = 3$ we can mimic the calculation found in Appendix C and apply Theorem 3.13 to get a stability result. We first define

three sets $\mathcal{A}$, $\mathcal{B}$ and $\mathcal{C}$ of inequalities.

$$\mathcal{A}: \quad c\beta_1 \le c\beta_2 + c\beta_3 + g_2 \qquad c\beta_1 \le 2c\beta_2 + k_3 + g_2 \qquad c\beta_3 \le c\beta_2 + g_2$$

$$\mathcal{B}: \quad g_3 \le k_2 + g_2 + b \qquad k_3 + g_3 \le k_2 + g_2 + b + \min\{c\beta_2, c\beta_3\}$$
$$k_2 + k_3 \le g_3 + b + c\beta_3 \qquad k_3 \le g_3 + b + \min\{k_1, g_3, c\beta_1\}$$
$$k_3 \le c\beta_1 + c\beta_2 + g_2 \qquad k_2 \le g_3 + b + \min\{k_3, c\beta_2\}$$

$$\mathcal{C}: \quad c\beta_1 \le k_3 + g_3 + b \qquad c\beta_2 \le k_3 + g_3 + b \qquad c\beta_3 \le 2g_3 + b$$
$$k_2 \le g_3 + b \qquad k_3 \le c\beta_2 + g_2 \qquad k_3 \le g_3 + b$$
$$k_3 + g_3 \le k_2 + g_2 + b$$

Theorem 8.9. *For $r = 3$, if $\mathcal{A}$ and either $\mathcal{B}$ or $\mathcal{C}$ are satisfied, and $\sigma > 1$ then every omega limit point of (8.2) is an equilibrium.*

Remark. (1) It should be noted that if we reintroduce the assumption $c\beta_m = c\beta$, $k_j = k$ for $j = 1, 2, 3$ and $g_2 = g_3 = g$, then if $k \le g + b$, we will have $\mathcal{A}$ and either $\mathcal{B}$ or $\mathcal{C}$ satisfied or $c\beta$ will be smaller than b in which case, the disease-free equilibrium is globally stable, as seen in Section 8.5.2..

(2) The requirement that $\mathcal{A}$ and either $\mathcal{B}$ or $\mathcal{C}$ be satisfied can be seen as a measure of the robustness of the conditions $k_1 = k_2 = k_3$, $g_2 = g_3$, $\beta_1 = \beta_2 = \beta_3$ and $k \le g + b$ which were used in Section 8.5.2. Theorem 8.9 implies that limited heterogeneity does not interfere with the fact that solutions to (8.2) limit to an equilibrium.

Conjecture 8.10. *For any r, if $\sigma \le 1$ then P_0 is globally stable in Γ_r under (8.2) and if $\sigma > 1$ then there is a unique endemic equilibrium P_* which is globally asymptotically stable in $\Gamma_r \setminus P_0$.*

8.6 The Dynamics of the Population Sizes

Recalling that $N = S + I_1 + \cdots + I_r$, equation (8.1) implies

$$N' = (b - k_r i_r - d)N \tag{8.13}$$

where d may depend on the state variables $s, i_1, \ldots, i_r$ and N. If Conjecture 8.10 is true, then $(s, i_1, \ldots, i_r)$ limits to a constant value $(s_*, i_{1*}, \ldots, i_{r*})$ and so (8.13) limits to

$$N' = (b - k_r i_{r*} - d_*(N))N \tag{8.14}$$

where $d_*(N) = d(s_*, i_{1*}, \ldots, i_{r*}, N)$ is non-negative.

We now make some assumptions about the form of d. To avoid unbounded growth, we assume that d is larger than b if N is sufficiently large. Then, by (8.13), there is an upper bound on the size of N. It is also reasonable to assume that in the absence of disease, a small population would grow. ie. $d(1, 0, \ldots, 0, N) < b$ for N sufficiently small.

A simple and plausible form for d is that d depends only on N and that $d(N)$ increases monotonely with N. Suppose $d(N) = d_0 N$ for some constant $d_0 > 0$. Then (8.14) becomes the logistic equation

$$N' = (b - k_r i_{r*} - d_0 N)N.$$

This equation has equilibria at $N_0 = 0$ and $N_1 = \frac{b - k_r i_{r*}}{d_0}$. If $b - k_r i_{r*} \leq 0$ then N_0 is globally stable and the total population dies out. Otherwise, N_1 attracts all positive solutions, and the original system (8.1) goes to the equilibrium $(s_*, i_{1*}, \ldots, i_{r*})N_1$. In summary, we state the following.

Theorem 8.11. *Suppose that a solution of (8.2) limits to an equilibrium with $i_r = i_{r*}$. Also, suppose that $d = d_0 N$. Then $\lim_{t \to \infty} N(t) = max\{\frac{b - k_r i_{r*}}{d_0}, 0\}$.*

8.7 Discussion

Let us return to the case $r = 3$ and assume that $\beta_1 = \beta_2 = \beta_3$. Then it can be shown that $\frac{\partial \sigma}{\partial g_2}, \frac{\partial \sigma}{\partial g_3} > 0$. A consequence of this is that by treating individuals, we may destabilize the disease-free equilibrium. The reason for this may be that through treatment, we are increasing the expected available time for transmission of the virus. This assumes that there is no change in the behavior of the individual upon learning that he/she is HIV+.

On the other hand, if $g_2 = 0$ and β_2 is sufficiently small compared to β_3, then we can show that $\frac{\partial \sigma}{\partial g_3} < 0$. This means that treating those with low T4 cell counts may stabilize the disease-free equilibrium. The condition $g_2 = 0$ means that treated individuals will not return to the initial stage of infection for which the infectivity is quite high. The assumption on β_2 and β_3 may reflect reality quite well since it is known that individuals infected with HIV undergo a long period during which their infectivity is quite low before it climbs [27].

8.8 Conclusions

If the threshold parameter $\sigma < 1$ then the disease dies out near the disease-free equilibrium. If $\sigma > 1$ then the disease persists and there exists at least one endemic equilibrium.

For two infective stages, every omega limit point is an equilibrium.

For three infective stages, if $k_m = k$ and $\beta_m = \beta$ for $m = 1, 2, 3$ and $g_m = g$ for $m = 2, 3$ then there is a unique endemic equilibrium for $\sigma > 1$ and there are no endemic equilibria for $\sigma \leq 1$. If $k \leq g + b$ and $\sigma > 1$, then the endemic equilibrium attracts all solutions except the disease-free equilibrium.

CHAPTER 9

The MSEIR Model

9.1 Introduction

A standard model for disease transmission is the SEIR model where the population is divided into susceptible, exposed, infective and recovered classes. The sizes of these classes are respectively S, E, I and R. For the standard SEIR model [35, 37], recruitment of new individuals is into the susceptible class. Individuals in the infective class may or may not undergo disease related death, depending on the disease. This model is applicable for diseases which confer a permanent immunity, as once an individual has recovered, the individual will not become susceptible again. The transfer diagram follows.

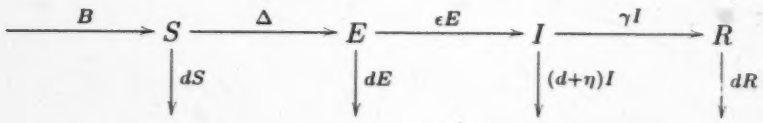

Figure 9.1: Transfer diagram for the SEIR model.

The recruitment B may be constant or a function of the total population size $N = S + E + I + R$. The incidence may be $\Delta = \beta SI$ if mass action is used or $\Delta = \beta SI/N$ if proportional mixing is used, or may take more general forms such as $\Delta = \beta S^q I^p$.

For those individuals that progress from E to I or from I to R, we have assumed an exponential distribution of waiting times with mean waiting times $\frac{1}{\epsilon}$ and $\frac{1}{\gamma}$ respectively [22]. The non-disease related death rate is d. Individuals in the infective class have an additional death rate ηI where $\eta \geq 0$.

In [35], Li et al. resolve the existence of equilibria and their local stability for the SEIR model with $B = bN$ and mass action. Global stability is shown for $\eta < \epsilon$. In [37], Li and Muldowney study the existence and local stability of equilibria for $B = d$, $\eta = 0$ and $\Delta = \beta S^q I^p$. Global stability is shown for $p \leq 1$, which includes the case when mass action is used.

For some diseases, including measles, rubella and mumps, women who have been infected transfer antibodies across the placenta so that their newborn children temporarily have what is called passive immunity. With this in mind, we now introduce the MSEIR model as developed by Hethcote in [22]. The size of the group possessing passive immunity is M. The transfer diagram is below.

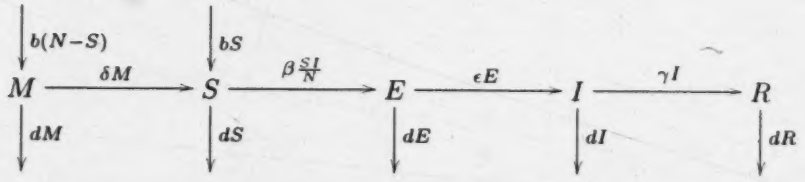

Figure 9.2: Transfer diagram for the MSEIR model.

Recruitment of new individuals into the population is proportional to the total population $N = M+S+E+I+R$. We assume that all newborns have a temporary passive immunity, except for those born of susceptible mothers. Using proportional mixing, the incidence is $\Delta = \beta SI/N$ where β is the average number of contacts per unit time per person. We assume an exponential distribution of waiting times in groups M, E and I with mean waiting times $\frac{1}{\delta}$, $\frac{1}{\epsilon}$ and $\frac{1}{\gamma}$ respectively. The natural death rate of the population is d.

The system of differential equation for the sizes of the groups is

$$\begin{aligned} M' &= b(N-S) - (\delta + d)M \\ S' &= bS + \delta M - \beta S\frac{I}{N} - dS \\ E' &= \beta S\frac{I}{N} - (\epsilon + d)E \\ I' &= \epsilon E - (\gamma + d)I \\ R' &= \gamma I - dR \end{aligned} \tag{9.1}$$

with

$$N' = (b-d)N.$$

Because (9.1) is homogeneous of degree 1, it is convenient to switch to proportional variables, which describe the fractions in each group. Letting $(m, s, e, i, r) = \frac{1}{N}(M, S, E, I, R)$ we get

$$\begin{aligned} m' &= b(1-s) - (\delta + b)m \\ s' &= \delta m - \beta si \\ e' &= \beta si - (\epsilon + b)e \\ i' &= \epsilon e - (\gamma + b)i \end{aligned} \tag{9.2}$$

where the differential equation for r has been omitted since r can be determined from the equation $r = 1 - m - s - e - i$. We are interested in the dynamics described by (9.2) on the set $D = \{(m, s, e, i) \in \mathbb{R}^4_{\geq 0} : m + s + e + i \leq 1\}$.

In [22] the threshold parameter σ has been calculated to be

$$\sigma = \frac{\beta\epsilon}{(\gamma + b)(\epsilon + b)}.$$

If $\sigma \leq 1$ then the disease-free equilibrium $P_0 = (0, 1, 0, 0)$ is globally asymptotically stable. If $\sigma > 1$ then P_0 is unstable, the disease is uniformly persistent and there is a unique endemic equilibrium $P_* \in D$ which is locally asymptotically stable. The

global stability for $\sigma > 1$ is unresolved. We now give a global stability result for $\delta \geq \epsilon + b$. The problem remains unsolved for $\delta < \epsilon + b$.

9.2 Global Stability

Proposition 9.1. *If $\sigma > 1$ and $\delta \geq \epsilon + b$ then P_* is globally asymptotically stable.*

Proof. Suppose $\sigma > 1$. Because the system is persistent and D is positively invariant, there exists a compact set K which is absorbing in the interior of D. In fact K is absorbing in $D \setminus P_0$.

Let the Jacobian of (9.2) be denoted by $\frac{\partial f}{\partial x}$. Then

$$\frac{\partial f}{\partial x} = \begin{bmatrix} -(\delta + b) & -b & 0 & 0 \\ \delta & -\beta i & 0 & -\beta s \\ 0 & \beta i & -(\epsilon + b) & \beta s \\ 0 & 0 & \epsilon & -(\gamma + b) \end{bmatrix}$$

and the second compound is given by

$$\frac{\partial f}{\partial x}^{[2]} = -\operatorname{diag}\begin{pmatrix} \delta + b + \beta i \\ \delta + \epsilon + 2b \\ \delta + \gamma + 2b \\ \epsilon + b + \beta i \\ \gamma + b + \beta i \\ \epsilon + \gamma + 2b \end{pmatrix} + \begin{bmatrix} 0 & 0 & -\beta s & 0 & 0 & 0 \\ \beta i & 0 & \beta s & -b & 0 & 0 \\ 0 & \epsilon & 0 & 0 & -b & 0 \\ 0 & \delta & 0 & 0 & \beta s & \beta s \\ 0 & 0 & \delta & \epsilon & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta i & 0 \end{bmatrix}$$

[see Appendix A]. Let

$$Q = \begin{bmatrix} \frac{1}{e} & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{e} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{e} & 0 & 0 \\ 0 & 0 & \frac{1}{\alpha i} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\alpha i} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\alpha i} \end{bmatrix}$$

where α is a constant slightly larger than 1. We are interested in the stability of

the matrix $M = Q_f Q^{-1} + Q\frac{\partial f}{\partial x}^{[2]} Q^{-1}$. Explicitly,

$$M = -\text{diag}\begin{pmatrix} \delta + b + \beta\frac{si}{e} - \epsilon \\ \delta + b + \beta\frac{si}{e} \\ \beta i + \beta\frac{si}{e} \\ \delta + b + \epsilon\frac{e}{i} \\ \beta i + \epsilon\frac{e}{i} \\ \epsilon + b + \epsilon\frac{e}{i} \end{pmatrix} + \begin{bmatrix} 0 & 0 & 0 & -\alpha\beta\frac{si}{e} & 0 & 0 \\ \beta i & 0 & -b & \alpha\beta\frac{si}{e} & 0 & 0 \\ 0 & \delta & 0 & 0 & \alpha\beta\frac{si}{e} & \alpha\beta\frac{si}{e} \\ 0 & \frac{1}{\alpha}\epsilon\frac{e}{i} & 0 & 0 & -b & 0 \\ 0 & 0 & \frac{1}{\alpha}\epsilon\frac{e}{i} & \delta & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta i & 0 \end{bmatrix}. \tag{9.3}$$

In Appendix D, it is shown that for $\delta \geq \epsilon + b$, there is a Lozinskii measure μ such that $\mu(M) < 0$ on K. This means that q_2 as defined in equation (3.9) is negative. Thus, by Theorem 3.6, P_* is globally asymptotically stable in $D \setminus P_0$. □

Remarks. (1) It is shown in [22] that P_* is given by

$$(m_*, s_*, e_*, i_*) = (1 - \frac{1}{\sigma}) \cdot \Big(\frac{b}{\delta + b}, \frac{1}{\sigma - 1}, \frac{\delta b}{(\delta + b)(\epsilon + b)}, \frac{\epsilon\delta b}{(\epsilon + b)(\delta + b)(\gamma + b)}\Big).$$

Thus, the condition $\delta \geq \epsilon + b$, used in Proposition 9.1, is equivalent to $e_* \geq m_*$.

(2) Typically, the duration of passive immunity is between six and twelve months. Typical latent periods are between one day and two weeks. Since the rate constants are inversely proportional to the waiting times in the various classes [22], we see that δ is generally much smaller than ϵ. Thus, for most diseases, it is unlikely that the condition $\delta \geq \epsilon + b$ is satisfied.

9.3 Conclusions

If $\sigma < 1$ then the disease will die out regardless of starting conditions. No matter how much disease is introduced into a population, the disease will not be able to successfully invade. Eventually, the population will consist entirely of susceptibles.

If $\sigma > 1$ then any small amount of disease introduced to the population will persist. Also, there exists a unique endemic equilibrium. If $\delta \geq \epsilon + b$ then the disease will approach the endemic equilibrium proportions in the population.

CHAPTER 10

Conclusions and Recommendations

Often, various compartment models of the form given in equation (1.1), describe different systems which exhibit similar dynamics. Thus, it should be possible to determine certain underlying assumptions to which this behaviour can be attributed. For instance, by studying equation (1.1) with the assumption that the Jacobian matrix has a certain sign structure, it is sometimes possible to determine information about the stability of endemic equilibria without knowing the exact quantities. By analyzing the implications of certain general assumptions, it may be possible to make statements about real-world situations for which exact equations are difficult to determine. A difficulty in this approach, is that many of the standard techniques for stability analysis require calculations for which it is necessary to know quantities exactly.

While the strategy presented in Chapter 2 is a good first step in developing a constructive approach to finding non-absolute norms to use as Lyapunov functions, the class of norms which are constructed using that strategy are limited. It should be noted, though, that the strategy outlined there leads, as in the given examples, to exact values for the Lozinskii measures corresponding to various norms. To our knowledge, exact Lozinskii measures have not previously been calculated for non-absolute norms. An algorithm for constructing more general Lyapunov functions should be developed.

In order to study dynamical systems on invariant manifolds in the same manner that general dynamical systems are studied, it is necessary to develop an analogue of Theorem 3.7 for invariant manifolds. This would allow Theorem 3.11 to be generalized more seamlessly to the context of invariant manifolds rather than

taking the form of Theorem 3.17, for which it is necessary to assume that (3.19) holds on the boundary and the interior of the set D rather than just on the interior of D.

It was observed in Chapter 1 that the models considered here are relatively crude predictors for the long-term behaviour of the disease. They are qualitative in nature and an attempt to match the model with a specific occurrence of a disease would be futile in any prediction of fine local dynamics. Nevertheless, they can have value in predicting the ultimate tendencies within limitations imposed by the various simplifying assumptions in the model. Public policy decisions on issues such as medication, vaccination and hygiene might be based on insight into the consequences for the exposure of individuals to infection, recovery or amelioration rates provided by these analyses. If $R_0 = 1$ or $\sigma = 1$ is proven to be a strict threshold, then it points to parameters to target for disease eradication. An appraisal of the validity of the various models might be based on observation of the behaviour of different outbreaks. For example, variations in the behaviour of epidemics in locations with different values for parameters such as the natural death rate should be predictable by valid models of this type. Failure to predict observed stable behaviour would obviously call the fundamental assumptions into question.

The model of the interaction between cystic fibrosis and typhoid fever studied in Chapter 5 is a variation of the SIS model for which individuals who recover from the infectious disease immediately become susceptible again. It would be more realistic to model this interaction by using a SIRS model for which there is a recovered stage that individuals pass through before becoming susceptible again. It is anticipated that this analysis would reveal behaviour similar to that found for the SIS model.

In studying the global stability of the MSEIR model, it is shown that for $\sigma > 1$,

the endemic equilibrium is globally stable if $\delta \geq \epsilon + b$. Biologically, this means that if the rate at which individuals lose passive immunity is greater than the sum of the rate at which individuals leave the exposed class for the infective class and the birth rate, then the system will go to a constant steady state for which there is a fixed proportion of the population in each of the population classes. The global stability remains unresolved for $\sigma > 1$, $\delta < \epsilon + b$ or, in other words, the long-term behaviour of the disease level in the population is unknown for the case when the disease persists in the population and the loss of passive immunity is sufficiently slow. Likely, the endemic equilibrium is globally stable for all parameter values, but the approach used in this thesis has not been able to demonstrate this. In order to progress further on this problem with the method of compound matrices, it is necessary to develop the techniques further. While the theory seems sufficiently advanced to study these problems, the calculations often yield only partial solutions. The difficulty in the case where $\delta < \epsilon + b$ arises from a positive term on the main diagonal of the second compound matrix. Often, positive diagonal terms can be removed by considering a matrix Q as it appears in equations (3.8) and (3.9). This method has not lead to a solution in this case. Another approach may be necessary.

The main mathematical innovation of this thesis may be the approach developed in Section 3.4. The work of Li and Muldowney [40] shows how dynamics on an invariant manifold may be analyzed without the use of special coordinate systems. The calculations, however, are affected by the behaviour of the underlying dynamics in a neighbourhood of the manifold. The observation is that infinitely many systems have the same dynamics on the manifold and it brings into play $n \times m$ arbitrary functions that may be used to optimize and simplify the resulting expression (3.26). Here n is the dimension of the space in which the manifold is embedded and m is the co-dimension of the manifold.

Bibliography

[1] R. M. Anderson, R. M. May, *Vaccination against rubella and measles: Qualitative investigations of different policies*, J. Hyg. Camb. 90 (1983) 259-325.

[2] R. M. Anderson, R. M. May, eds., *Population Biology of Infectious Diseases*, Springer-Verlag, Berlin, Heidelberg, New York, 1982.

[3] R. M. Anderson, R. M. May, *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, 1991.

[4] D. Baltimore, *Lessons from people with nonprogressive HIV infection*, N. Engl. J. Med. 332 (1995) 259-260.

[5] K. Beck, *A model of the population genetics of cystic fibrosis in the United States*, Math. Biosci. 58 (1982) 243-257.

[6] K. Beck, J. P. Keener, P. Ricciardi, *The effect of epidemics on genetic evolution*, J. Math. Biol. 19 (1984) 79-94.

[7] I. Bendixson, *Sur les curbes définiés par des équations différentielles*, Acta Math. 24 (1901) 1-88.

[8] S. Busenberg, P. van den Driessche, *Analysis of a disease transmission model in a population with varying size*, J. Math. Biol. 28 (1990) 257-270.

[9] S. Busenberg, P. van den Driessche, *A method for proving the nonexistence of limit cycles*, J. Math. Anal. Appl. 172 (1993) 463-479.

[10] Y. Cao, L. Qin, L. Zhang, J. Safrit, D. D. Ho, *Virologic and immunologic characterization of long-term survivors of HIV type 1 infection*, N. Engl. J. Med. 332 (1995) 201-208.

[11] W. A. Coppel, *Stability and asymptotic behavior of differential equations*, Heath, Boston, 1965.

[12] H. Dulac, *Recherche des cycles limites*, C. R. Acad. Sci. Paris 204 (1937) 1703-1706.

[13] O. Diekmann, J. A. P. Heesterbeek, J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio $\mathbb{R}_0$ in models for infectious diseases in heterogeneous populations*, J. Math. Biol. 28 (1990) 365-382.

[14] N. M. Ferguson, D. J. Nokes, R. M. Anderson, *Dynamical complexity in age-structured models of the transmission of measles virus: Epidemiological implications of high levels of vaccine uptake*, Math. Biosci. 138 (1996) 101-130.

[15] L. Q. Gao, J. Mena-Lorca, H. W. Hethcote, *Variations on a theme of SEI endemic models*, in Differential Equations and Applications to Biology and to Industry, M. Martelli et al., eds., World Scientific Publishing, Singapore, 1996, 191-207.

[16] K. P. Hadeler, *Periodic solutions of homogeneous equations*, J. Differential Equations 95 (1992) 183-202.

[17] J. K. Hale, *Ordinary differential equations*, John Wiley & Sons, New York, 1969.

[18] M. E. Halloran, S. L. Cochi, T. A. Lieu, M. Wharton, L. Fehrs, *Theoretical epidemiologic and morbidity effects of routine varicella immunization of preschool children in the United States*, Am. J. Epidemiol. 140 (1994) 81-104.

[19] W. H. Hamer, *Epidemic disease in England*, Lancet 1 (1906) 733-739.

[20] P. Hartman, *Ordinary Differential Equations*, Birkhauser, Boston, 1982.

[21] H. W. Hethcote, *Optimal ages of vaccination for measles*, Math. Biosci. 89 (1988) 29-52.

[22] H. W. Hethcote, *The mathematics of infectious diseases*, SIAM Review 42 (2000) 599-653.

[23] H. W. Hethcote, J. W. Van Ark, *Modeling HIV transmission and AIDS in the United States*, Springer-Verlag, Berlin, 1992.

[24] M. W. Hirsch, *Differential Topology*, Springer-Verlag, NewYork, 1990.

[25] J. Hofbauer, K. Sigmund, *Evolutionary games and population dynamics*, Cambridge University Press, Cambridge, 1998.

[26] W. Huang, K. L. Cooke, C. Castillo-Chavez, *Stability and bifurcation for a multiple group model for the dynamics of HIV/AIDS transmission*, SIAM J. Appl. Math. 52 (1992) 835-854.

[27] J. M. Hyman, J. Li, E. A. Stanley, *The differential infectivity and staged progression models for the transmission of HIV*, Math. Biosci. 155 (1999) 77-109.

[28] J. T. Kemper, *On the identification of superspreaders for infectious disease*, Math. Biosci. 48 (1980) 111-127.

[29] J. T. Kemper, *The evolutionary effect of endemic infectious disease: continuous models for an invariant pathogen*, J. Math. Biology 15 (1982) 65-77.

[30] W. O. Kermack, A. G. McKendrick, *Contributions to the mathematical theory of epidemics, part 1*, Proc. Roy. Soc. London Ser. A 115 (1927) 700-721.

[31] J. P. Lasalle, *The stability of dynamical systems*, Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1976.

[32] M. Y. Li, *Geometrical studies on the global asymptotic behaviour of dissipative dynamical systems*, Ph.D. thesis, University of Alberta (1993).

[33] M. Y. Li, *Bendixson's Criterion for autonomous systems with an invariant linear subspace*, Rocky Mount. J. Math. 25 (1995) 351-363.

[34] M. Y. Li, *Dulac criteria for autonomous systems having an invariant affine manifold*, J. Math. Anal. Appl. 199 (1996) 374-390.

[35] M. Y. Li, J. R. Graef, L. Wang, J. Karsai, *Global dynamics of a SEIR model with varying total population size*, Math. Biosci. 160 (1999) 191-213.

[36] M. Y. Li, J. S. Muldowney, *On R. A. Smith's autonomous convergence theorem*, Rocky Mount. J. Math. 25 (1995) 365-379.

[37] M. Y. Li, J. S. Muldowney, *Global stability for the SEIR model in epidemiology*, Math. Biosci. 124 (1995) 155-164.

[38] M. Y. Li, J. S. Muldowney, *A geometric approach to global-stability problems*, SIAM J. Math. Anal. 27 (1996) 1070-1083.

[39] M. Y. Li, J. S. Muldowney, *Phase asymptotic semiflows, Poincare's condition and the existence of stable limit cycles*, J. Differential Equations 124 (1996) 425-448.

[40] M. Y. Li, J. S. Muldowney, *Dynamics of differential equations on invariant manifolds*, J. Differential Equations 168 (2000) 295-320.

[41] M. Y. Li, J. S. Muldowney, P. van den Driessche, *Global stability for the SEIRS models in epidemiology*, Canadian Appl. Math. Quart. 7 (1999) 409-425.

[42] Y. Li, J. S. Muldowney, *On Bendixson's Criterion*, J. Differential Equations 106 (1993) 27-39.

[43] X. Lin, H. W. Hethcote, P. van den Driessche, *An epidemiological model for HIV/AIDS with proportional recruitment*, Math. Biosci. 118 (1993) 181-195.

[44] I. M. Longini Jr. *Models of the interaction of host genotypes and infectious disease*, Mathematics in Biology and Medicine (S. Levin, ed.), Lect. Notes in Biomath. 57, Springer-Verlag, Berlin-Heidelberg-New York-Tokyo (1985) 158-163.

[45] R. H. Martin Jr., *Logarithmic norms and projections applied to linear differential systems*, J. Math. Anal. Appl. 45 (1974) 432-454.

[46] C. C. McCluskey, J. S. Muldowney, *Stability implications of Bendixson's Criterion*, SIAM Review 40 (1998) 931-934.

[47] J. S. Muldowney, *Compound matrices and ordinary differential equations*, Rocky Mount. J. Math. 20 (1990) 857-871.

[48] T. R. O'Brien, W. A. Blattner, D. Waters, M. E. Eyster, M. W. Hilgartner, A. R. Coher, N. Luban, A. Hatzakis, L. M. Aledort, P. S. Rosenbert, W. J. Milet,

B. L. Kroner, J. J. Goedert, *Serum HIV-1 RNA levels and time to development of AIDS in the multicenter hemophilia cohort study*, JAMA 276 (1996) 105-110.

[49] G. B. Pier, M. Grout, T. Zaidi, G. Meluleni, S. S. Mueschenborn, G. Banting, R. Ratcliff, M. J. Evans, W. H. Colledge, *Salmonella typhi uses CFTR to enter intestinal epithelial cells*, Nature 393 (1998) 79-82.

[50] C. C. Pugh, *The closing lemma*, Amer. J. Math. 89 (1967) 956-1009.

[51] C. C. Pugh, C. Robinson, *The C^1 closing lemma including Hamiltonians*, Ergodic Theory Dynam. Systems 3 (1983) 251-313.

[52] R. Ross, *The prevention of malaria*, Murray, London, second edition, 1911.

[53] M. C. Schuette, H. W. Hethcote, *Modeling the effects of varicella vaccination programs on the incidence of chickenpox and shingles*, Bull. Math. Biol. 61 (1999) 1031-1064.

[54] C. P. Simon, J. A. Jacquez, *Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations*, SIAM J. Appl. Math. 52 (1992) 541-576.

[55] M. Spivak, *Calculus on manifolds*, W. A. Benjamin, Inc., New York, 1965.

[56] H. R. Thieme, *Persistence under relaxed point-dissipativity (with an application to an endemic model*, SIAM J. Math. Anal. 24 (1993) 407-435.

[57] P. van den Driessche, J Watmough, A simple SIS epidemic model with a backward bifurcation, J. Math. Biol. 40 (2000) 525-540.

[58] M. T. Wong, M. J. Dolan, E. Kozlow, R. Doe, G. P. Melcher, D. S. Burke, R. N. Boswell, M. Vahey, *Patterns of virus burden and T cell phenotype are established early and are correlated with the rate of disease progression in HIV type 1 infected persons*, J. Infect. Dis. 173 (1996) 877-887.

Appendix A

Compound Matrices

Let $x = (x_1, \ldots, x_n)^T \in \mathbb{R}^n$. We will think of x as representing the line segment connecting the origin to the point x. Each x_i is the oriented length of the projection of x onto the ith coordinate axis.

Let $x^1, \ldots, x^k \in \mathbb{R}^n$ where $x^r = (x_1^r, \ldots, x_n^r)^T$ for $r = 1, \ldots, k$. Then a k-dimensional volume z is induced. Geometrically, z can be thought of as representing the parallelepiped spanned by the x^r. In this sense, z is equivalent to the set $\{\alpha_1 x^1 + \cdots + \alpha_k x^k : \alpha_r \in [0,1], r = 1, \ldots, k\}$.

For every $I = (i_1, \ldots, i_k)$ satisfying $1 \leq i_1 < \cdots < i_n \leq n$, we define

$$z_I = \det \begin{bmatrix} x_{i_1}^1 & \cdots & x_{i_1}^k \\ \vdots & & \vdots \\ x_{i_k}^1 & \cdots & x_{i_k}^k \end{bmatrix}. \tag{A.1}$$

Given a k-dimensional coordinate space which is spanned by the standard basis vectors $e^{i_1}, \ldots, e^{i_k}$, z_I represents the size of the projection of z onto the Ith coordinate space. Algebraically, z is the vector consisting of the z_I ordered lexicographically. We write $z = x^1 \wedge \cdots \wedge x^k$. The space of all linear combinations of such vectors is called the kth exterior product of $\mathbb{R}^n$ and is denoted by $\wedge^k \mathbb{R}^n$. This space is isomorphic to $\mathbb{R}^{\binom{n}{k}}$. This is equivalent to the conventional development of $\wedge^k \mathbb{R}^n$ found in [55], for example.

Note that it follows from equation (A.1) that z is linear in each x^r, so that $x^1 \wedge \cdots \wedge (ay + bw) \wedge \cdots \wedge x^k = a x^1 \wedge \cdots \wedge y \wedge \cdots \wedge x^k + b x^1 \wedge \cdots \wedge w \wedge \cdots \wedge x^k$. Equation (A.1) also implies that if x^r and x^s are interchanged for some $r, s \in \{1, \ldots, k\}$ then the sign of z changes.

Let $A \in M_{n\times n}$. Then A induces two linear operators on $\wedge^k\mathbb{R}^n$ (and $\mathbb{R}^{\binom{n}{k}}$) which are defined by

$$A^{(k)}\left(x^1 \wedge \cdots \wedge x^k\right) = (Ax^1) \wedge \cdots \wedge (Ax^k) \tag{A.2}$$

and

$$A^{[k]}\left(x^1 \wedge \cdots \wedge x^k\right) = (Ax^1) \wedge \cdots \wedge x^k + \ldots + x^1 \wedge \cdots \wedge (Ax^k). \tag{A.3}$$

These operators are called the kth multiplicative compound of A and the kth additive compound of A, respectively. We use $A^{(k)}$ to denote both the operator which is the kth multiplicative compound of A and the matrix associated with the operator. Similarly, $A^{[k]}$ is used to refer to both the operator and the associated matrix for the additive compound. Each of $A^{(k)}$ and $A^{[k]}$ has size $\binom{n}{k} \times \binom{n}{k}$ and depends continuously on A. The names come from the easily shown properties that $(AB)^{(k)} = A^{(k)}B^{(k)}$ and $(A+B)^{[k]} = A^{[k]} + B^{[k]}$.

Proposition A.1. *Let $\lambda_1, \ldots, \lambda_k$ be eigenvalues of A with corresponding eigenvectors $x^1, \ldots, x^k$. Let $z = x^1 \wedge \cdots \wedge x^k$. Then $\prod_{r=1}^k \lambda_r$ is an eigenvalue of $A^{(k)}$ with eigenvector z and $\sum_{r=1}^k \lambda_r$ is an eigenvalue of $A^{[k]}$, also with eigenvector z.*

Proof. This follows from equations (A.2) and (A.3) and the fact that z is multilinear in $x^1, \ldots, x^k$. □

In fact, the set of $\binom{n}{k}$ eigenvalues of $A^{(k)}$ consists exactly of the products of k-tuples of eigenvalues of A and the eigenvalues of $A^{[k]}$ consist of the sums of k-tuples of eigenvalues of A. If the eigenvalues of A are distinct, then this follows immediately from Proposition A.1. Otherwise, we consider perturbations of A and use the fact that the eigenvalues depend continuously on the elements of the matrix.

We now determine what the matrices associated with the compounds look like. Let E^I be the Ith (in the lexicographical ordering) standard basis vector in $\wedge^k \mathbb{R}^n$. Using equation (A.1) it can be shown that

$$E^I = e^{i_1} \wedge \cdots \wedge e^{i_k}.$$

If $z = A^{(k)} E^I$ then z is the Ith column of $A^{(k)}$. Similarly, letting $y^r = Ae^r$ we see that y^r is the rth column of A. Thus, by (A.2), the Ith column of $A^{(k)}$ is equal to the exterior product of columns $i_1, \ldots, i_k$ of A.

Let $J = (j_1, \ldots, j_k)$ where $1 \leq j_1 < \cdots < j_k \leq n$ and let $A_{IJ}^{(k)}$ be the IJ entry of $A^{(k)}$. Then by (A.1),

$$A_{IJ}^{(k)} = \det \begin{bmatrix} y_{j_1}^{i_1} & \cdots & y_{j_1}^{i_k} \\ \vdots & & \vdots \\ y_{j_k}^{i_1} & \cdots & y_{j_k}^{i_k} \end{bmatrix}.$$

Thus, the kth multiplicative compound is the matrix formed by taking the determinant of each of the $k \times k$ submatrices of the original matrix. It follows that $A^{(1)} = A$ and $A^{(n)} = \det(A)$.

We now determine $A_{IJ}^{[k]}$, the IJ entry of $A^{[k]}$.

$$\begin{aligned} A_{IJ}^{[k]} &= \left(A^{[k]} E^I\right)_J \\ &= \left(\sum_{r=1}^{k} e^{i_1} \wedge \cdots \wedge \left(Ae^{i_r}\right) \wedge \cdots \wedge e^{i_k}\right)_J \\ &= \sum_{r=1}^{k} \left(e^{i_1} \wedge \cdots \wedge y^{i_r} \wedge \cdots \wedge e^{i_k}\right)_J \\ &= \sum_{r=1}^{k} \det B_{IJ,r} \end{aligned}$$

where

$$B_{IJ,r} = \begin{bmatrix} e_{j_1}^{i_1} & \cdots & y_{j_1}^{i_r} & \cdots & e_{j_1}^{i_k} \\ \vdots & & \vdots & & \vdots \\ e_{j_k}^{i_1} & \cdots & y_{j_k}^{i_r} & \cdots & e_{j_k}^{i_k} \end{bmatrix}.$$

Note that $e_{j_v}^{i_u}$ equals one if $i_u = j_v$ and is zero otherwise. If I and J differ by two or more elements, then each $B_{IJ,r}$ has a column of zeroes and so $A_{IJ}^{[k]}$ is zero. Suppose I and J differ by exactly one element: say $i_u \notin J$ and $j_v \notin I$. Then for $r \neq u$, the uth column of $B_{IJ,r}$ consists entirely of zeroes. On the other hand, $B_{IJ,u} = (-1)^{u+v} y_{j_v}^{i_u}$. The sign of $B_{IJ,u}$ is given by the number of row and column interchanges necessary to move the entry $y_{j_v}^{i_u}$ from its starting place to the top left hand corner of the matrix. Finally, in the case that $I = J$, each $B_{IJ,r}$ consists of $(k-1)$ columns of the identity matrix plus one more column giving $B_{II,r} = y_{i_r}^{i_r}$. Thus,

$$A_{IJ}^{[k]} = \left\{ \begin{array}{cc} y_{i_1}^{i_1} + \cdots + y_{i_k}^{i_k} & \text{if } I = J \\ (-1)^{u+v} y_{j_v}^{i_u} & \text{if } I \text{ and } J \text{ differ by exactly one element: } i_u \notin J, j_v \notin I \\ 0 & \text{if } I \text{ and } J \text{ differ by two or more elements} \end{array} \right\}.$$

From this we can determine that $A^{[1]} = A$ and $A^{[n]} = \text{tr}\ (A)$.

Examples of Additive Compound Matrices

We present the matrices $A^{[k]}$ for $1 \leq k \leq n$ where A is an $n \times n$ matrix for $n = 2, 3, 4$. If $n = 1$, then A is a scalar and its only additive compound is $A^{[1]} = A$.

$n = 2$:

$$A^{[1]} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = A$$

$$A^{[2]} = a_{11} + a_{22} = \text{tr}\ (A)$$

$n = 3$:

$$A^{[1]} = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix} = A$$

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}$$

$$A^{[3]} = a_{11} + a_{22} + a_{33} = \text{tr } (A)$$

$n = 4$:

$$A^{[1]} = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22} & a_{23} & a_{24} \\ a_{31} & a_{32} & a_{33} & a_{34} \\ a_{41} & a_{42} & a_{43} & a_{44} \end{bmatrix} = A$$

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & a_{24} & -a_{13} & -a_{14} & 0 \\ a_{32} & a_{11} + a_{33} & a_{34} & a_{12} & 0 & -a_{14} \\ a_{42} & a_{43} & a_{11} + a_{44} & 0 & a_{12} & a_{13} \\ -a_{31} & a_{21} & 0 & a_{22} + a_{33} & a_{34} & -a_{24} \\ -a_{41} & 0 & a_{21} & a_{43} & a_{22} + a_{44} & a_{23} \\ 0 & -a_{41} & a_{31} & -a_{42} & a_{32} & a_{33} + a_{44} \end{bmatrix}$$

$$A^{[3]} = \begin{bmatrix} a_{11} + a_{22} + a_{33} & a_{34} & -a_{24} & a_{14} \\ a_{43} & a_{11} + a_{22} + a_{44} & a_{23} & -a_{13} \\ -a_{42} & a_{32} & a_{11} + a_{33} + a_{44} & a_{12} \\ a_{41} & -a_{31} & a_{21} & a_{22} + a_{33} + a_{44} \end{bmatrix}$$

$$A^{[4]} = a_{11} + a_{22} + a_{33} + a_{44} = \text{tr } (A)$$

Compound Matrices and Linear Differential Equations

Suppose $x^1, \ldots, x^k$ are solutions to

$$x' = A(t)x \tag{A.4}$$

for some matrix valued function $A(t)$. Since each z_I is the sum of products, where each product involves a term from each x^i, the product rule for derivatives gives

$$\begin{aligned} z' &= (x^1)' \wedge \cdots \wedge x^k \;+\; \ldots \;+\; x^1 \wedge \cdots \wedge (x^k)' \\ &= (Ax^1) \wedge \cdots \wedge x^k \;+\; \ldots \;+\; x^1 \wedge \cdots \wedge (Ax^k) \\ &= A^{[k]}(t)\, z. \end{aligned} \tag{A.5}$$

If the $x^i(t)$ are regarded as oriented line segments in $\mathbb{R}^n$ which evolve in time as solutions of (A.4), then $z(t) = x^1(t) \wedge \cdots \wedge x^k(t)$ can be considered an oriented k-dimensional volume in $\mathbb{R}^n$. It is a vector quantity of dimension $\binom{n}{k}$ and evolves in time as a solution to (A.5).

Let $X(t)$ be a matrix consisting of columns $x^1(t), \ldots, x^n(t)$, each of which is a solution to equation (A.4). Then $z(t) = x^1(t) \wedge \cdots \wedge x^n(t) = \det\big(X(t)\big)$ is a solution to (A.5) for $k = n$. Recalling that the nth additive compound of a $n \times n$ matrix is its trace, we see that for $k = n$, equation (A.5) becomes the Jacobi equation

$$\frac{\mathrm{d}}{\mathrm{d}t} \det\big(X(t)\big) = \operatorname{tr}\,\big(A(t)\big)\, \det\big(X(t)\big).$$

Thus, in particular, the n-dimensional oriented volume determined by the oriented line segments $x^1(t), \ldots, x^n(t)$ evolves as a solution of the Jacobi equation.

Suppose $W(t)$ is a fundamental matrix for equation (A.4). Then any solution of (A.4) can be written as $W(t)c$ where c is a constant vector in $\mathbb{R}^n$. Let $c^r \in \mathbb{R}^n$ and $x^r(t) = W(t)c^r$ for $r = 1, \ldots, k$. Then $z(t) = (Wc^1) \wedge \cdots \wedge (Wc^k) = W^{(k)}(c^1 \wedge \cdots \wedge c^k)$

is a solution to equation (A.5). Therefore, $W^{(k)}(t)$ is a fundamental matrix of equation (A.5).

Compound Matrices and Non-Linear Differential Equations

Suppose

$$y' = f(y) \tag{A.6}$$

where $y \in \mathbb{R}^n$ and $f : \mathbb{R}^n \to \mathbb{R}^n$ is differentiable. Let $\gamma(t; y_0)$ be the solution to (A.6) passing through y_0 at $t = 0$. The $n \times n$ matrix

$$W(t) = \frac{\partial \gamma}{\partial y_0}(t; y_0)$$

satisfies $W(0) = I$ and is a fundamental matrix for the linear variational equation

$$x'(t) = \frac{\partial f}{\partial y}\big(\gamma(t; y_0)\big)\, x(t). \tag{A.7}$$

Therefore, the $\binom{n}{k} \times \binom{n}{k}$ matrix

$$W^{(k)}(t) = \frac{\partial \gamma}{\partial y_0}^{(k)}(t; y_0)$$

is a fundamental matrix for the compound equation

$$z'(t) = \frac{\partial f}{\partial y}^{[k]}\big(\gamma(t; y_0)\big)\, z(t) \tag{A.8}$$

for $k = 1, \ldots, n$.

Consider, for a fixed t, the map

$$y_0 \mapsto y_t = \gamma(t; y_0).$$

This gives

$$\begin{aligned} dy_t &= \frac{\partial y_t}{\partial y_0}\, dy_0 \\ &= \frac{\partial \gamma}{\partial y_0}(t; y_0)\, dy_0 \\ &= W(t)\, dy_0. \end{aligned} \tag{A.9}$$

Now letting t vary, we see that for a fixed dy_0, the vector dy_t is a solution to equation (A.7). This follows from $W(t)$ being a fundamental matrix for (A.7). Thus, an infinitesimal oriented line segment at y_0 evolves in time under the dynamics of (A.6) as a solution to (A.7). Therefore, if an exterior k-product $dy_0^{i_1} \wedge \cdots \wedge dy_0^{i_k}$ at y_0 evolves as

$$\begin{aligned} dy_t^{i_1} \wedge \cdots \wedge dy_t^{i_k} &= \frac{\partial \gamma}{\partial y_0}^{(k)}(t; y_0)\ dy_0^{i_1} \wedge \cdots \wedge dy_0^{i_k} \\ &= W^{(k)}(t)\ dy_0^{i_1} \wedge \cdots \wedge dy_0^{i_k} \end{aligned}$$

Thus, infinitesimal oriented k-dimensional volumes at y_0 evolve as solutions of (A.8).

Let $X(t)$ be a matrix consisting of columns $x^1(t), \ldots, x^n(t)$, each of which is a solution to equation (A.7). Then $z(t) = x^1(t) \wedge \cdots \wedge x^n(t) = \det\big(X(t)\big)$ is a solution to (A.8) for $k = n$. Thus, we see that for $k = n$, equation (A.8) becomes the Liouville equation

$$\frac{\mathrm{d}}{\mathrm{d}t} \det\big(X(t)\big) = \mathrm{tr}\, \Big(\frac{\partial f}{\partial y}\big(\gamma(t)\big)\Big)\ \det\big(X(t)\big).$$

Geometrically, this means that, under the dynamics of (A.6) infinitesimal oriented n-dimensional volumes evolve as solutions of the Liouville equation.

Appendix B

We now verify Theorem 5.1 which makes use of equation (5.4).

$$\begin{aligned} s_0' &= b(1-\frac{1}{2}s_1)^2 - c\beta s_0 i_0 + r i_0 + s_0\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big) \\ i_0' &= c\beta s_0 i_0 - r i_0 - \mu i_0 + i_0\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big) \\ s_1' &= b s_1(1-\frac{1}{2}s_1) + s_1\big(\mu i_0 - b(1-\frac{1}{4}s_1^2)\big). \end{aligned} \tag{5.4}$$

Theorem 5.1. *If $c\beta - r - b - \mu \leq 0$ then in Γ, $P_0 = (1,0,0)$ is the only equilibrium and is globally stable. If $c\beta - r - b - \mu > 0$ then the equilibria in Γ are given by P_0, $P_1 = (\frac{r+b}{c\beta-\mu}, \frac{c\beta-\mu-r-b}{c\beta-\mu}, 0)$ and $P_2 = (x_*, y_*, z_*)$ where $x_*, y_*, z_* > 0$. When $c\beta - r - b - \mu > 0$, P_2 attracts all solutions in the interior of Γ.*

First, we determine the number of equilibria that are present. Suppose that $s_1 = 0$. Then equation (5.4) reduces to (5.2) and we see that if $c\beta \leq r + b + \mu$ then P_0 is the only equilibrium. If $c\beta > r + b + \mu$, then P_1 is also an equilibrium. Suppose that $s_1 \neq 0$ and $i_0 = 0$. Then $s_1' = \frac{1}{2}bs_1^2(\frac{1}{2}s_1 - 1)$. This has no solution for $s_1 \in (0,1]$. If $s_0 = 0$ then $s_0' > 0$ and so there are no equilibria. Thus, P_0 and P_1 are the only boundary equilibria.

Suppose $s_0, i_0, s_1 > 0$. Equations (5.4.b) and (5.4.c) imply

$$0 = c\beta s_0 - r - \mu + \mu i_0 - b(1-\frac{1}{4}s_1^2) \tag{B.1}$$

and

$$0 = b(1-\frac{1}{2}s_1) + \mu i_0 - b(1-\frac{1}{4}s_1^2). \tag{B.2}$$

Subtracting (B.2) from (B.1), making the substitution $s_0 = 1 - i_0 - s_1$ and rearranging, we get

$$c\beta i_0 = (\frac{1}{2}b - c\beta)s_1 + c\beta - r - b - \mu \tag{B.3}$$

which is the equation of a straight line. This line passes through the points $(i_0, s_1) = (\frac{c\beta-r-b-\mu}{c\beta}, 0)$ and $(\frac{-r-\frac{1}{2}b-\mu}{c\beta}, 1)$. So, if $c\beta - r - b - \mu \leq 0$ then the straight line does not intersect the interior of Γ and so we find no new equilibria. Suppose on the other hand, that $c\beta - r - b - \mu > 0$. Then there is a line segment of (B.3) which intersects Γ. The endpoints of this segment are at $A = (\frac{c\beta-r-b-\mu}{c\beta}, 0)$ and $B = (0, \frac{c\beta-r-b-\mu}{c\beta-\frac{1}{2}b})$.

Consider the quantity $\frac{s_1'}{s_1} = \mu i_0 + \frac{1}{4}bs_1^2 - \frac{1}{2}bs_1$. This quantity is positive at A, negative at B and must be zero at all equilibria. Since this quantity is quadratic in s_1 on the line segment connecting A and B, there must be exactly one equilibrium lying on this line segment. Labeling this equilibrium P_2, we conclude that there is a unique equilibrium in the interior of Γ.

We now determine the global stability. Suppose that $c\beta - r - b - \mu \leq 0$. Notice that

$$\begin{aligned} i_0' &= i_0\Big(c\beta s_0 - r - \mu(s_0 + s_1) + b(\frac{1}{4}s_1^2 - 1)\Big) \\ &\leq i_0\Big(c\beta s_0 - r(s_0 + i_0) - \mu s_0 + bs_0\Big) \\ &\leq i_0 s_0\big(c\beta - r - b - \mu\big) - ri_0^2 \end{aligned}$$

and so i_0 goes to zero as t goes to infinity. Thus the differential equation for s_1 limits to $s_1' = \frac{1}{2}bs_1(\frac{1}{2}s_1 - 1)$ and so s_1 also goes to zero. Thus all solutions in Γ go to P_0.

Suppose that $c\beta - r - b - \mu > 0$. Equation (5.4) has Γ as a positively invariant manifold. Let $V = s_0 + i_0 + s_1 - 1$. Following equations (3.13) and (3.14), we get $V' = \big(\mu i_0 - b(1 - \frac{1}{4}s_1^2)\big)V$ and so $\nu = \mu i_0 - b(1 - \frac{1}{4}s_1^2)$. Let $M = U_f U^{-1} + U\frac{\partial f}{\partial x}^{[3]}U^{-1} - \nu$ where $U = \frac{1}{s_0 i_0 s_1}$. By Theorem 3.13, if $M < 0$ then there are no periodic orbits in

the interior of Γ. The Jacobian is given by

$$\frac{\partial f}{\partial x} = \begin{bmatrix} -c\beta i_0 + \nu & r - c\beta s_0 + \mu s_0 & b(\frac{1}{2}s_1 + \frac{1}{2}s_0 s_1 - 1) \\ c\beta i_0 & c\beta s_0 - r - \mu + \mu i_0 + \nu & \frac{1}{2}bi_0 s_1 \\ 0 & \mu s_1 & b(1 - s_1 + \frac{1}{2}s_1^2) + \nu \end{bmatrix}$$

and $\frac{\partial f}{\partial x}^{[3]} = \text{tr}\,(\frac{\partial f}{\partial x})$. Therefore,

$$\begin{aligned} M &= -\Big(\frac{s_0'}{s_0} + \frac{i_0'}{i_0} + \frac{s_1'}{s_1}\Big) + \text{tr}\,\Big(\frac{\partial f}{\partial x}\Big) - \big(\mu i_0 - b(1 - \frac{1}{4}s_1^2)\big) \\ &= -\frac{b(1 - \frac{1}{2}s_1^2) + ri_0}{s_0} + b\Big(1 - \frac{1}{2}s_1 + \frac{1}{4}s_1^2\Big) \\ &= -\frac{ri_0}{s_0} + b\frac{1}{s_0}\Big(\frac{1}{4}s_1^2(s_0 - 1) + (s_0 + s_1 - 1) - \frac{1}{2}s_0 s_1\Big) \end{aligned}$$

which is negative on the interior of Γ. Thus, any periodic orbits in Γ must intersect the boundary. In Γ, each of $\{i_0 = 0\}$ and $\{s_1 = 0\}$ are positively invariant and contain no periodic orbits. Solutions which begin in $\{s_0 = 0\}$ move to the interior of Γ. Thus, there are no periodic orbits which intersect the boundary of Γ. Since Γ admits a Poincare-Bendixson property, every omega limit set must contain an equilibrium. We note that rather than using compound matrix techniques to preclude periodic solutions to (5.4), Corollary 3.21 can be used.

We now determine the stability of the equilibria by considering the Jacobian matrix. By left multiplying $\frac{\partial f}{\partial x}$ by the left eigenvector $[1, 1, 1]$ we see that on Γ, ν is an eigenvalue. Let λ_1 and λ_2 be the other two eigenvalues. Note that ν describes behaviour normal to Γ whereas λ_1 and λ_2 describe behaviour in Γ.

At P_0, $\frac{\partial f}{\partial x}$ is upper triangular, $\nu = -b$ and we see that $\lambda_1 = 0$ and $\lambda_2 = c\beta - r - b - \mu > 0$. It is easily shown that the local unstable manifold is $\{i_0 = 0\}$ and $\{s_1 = 0\}$ is a center manifold along which, solutions approach the equilibrium.

At P_1, $\nu = \mu i_0 - b$. By considering blocks in $\frac{\partial f}{\partial x}$ it is clear that $\mu i_0 > 0$ is an eigenvalue, say λ_1. Since the trace of the matrix is the sum of the eigenvalues, we get $\lambda_2 = r + b + \mu - c\beta < 0$. Thus, P_1 is a hyperbolic saddle relative to the

dynamics in Γ. It is easily shown that the stable manifold of P_1 is contained in the set $\{s_1 = 0\}$.

At P_2, equations (B.1) and (B.2) apply. Using these equations and the relationship between the trace and eigenvalues we get

$$\begin{aligned}\lambda_1 + \lambda_2 &= \text{tr}\,(\frac{\partial f}{\partial x}) - \nu \\ &= c\beta(s_0 - i_0) - r - \mu + \mu i_0 + b(1 - s_1 + \frac{1}{2}s_1^2) + 2\nu \\ &= (\mu - c\beta)i_0 + \frac{1}{2}bs_1(s_1 - 1) \\ &< 0. \end{aligned} \tag{B.4}$$

We calculate the determinant of $\frac{\partial f}{\partial x}$ at P_2. Adding each of the other rows to the first and using equations (B.1) and (B.2) to simplify the second and third diagonal terms we see that

$$\begin{aligned}\det\Big(\frac{\partial f}{\partial x}(P_2)\Big) &= \begin{vmatrix} \nu & \nu & \nu \\ c\beta i_0 & \mu i_0 & \frac{1}{2}bi_0 s_1 \\ 0 & \mu s_1 & \frac{1}{2}bs_1(s_1 - 1) \end{vmatrix} \\ &= \nu\Big(\mu i_0 \frac{1}{2}bs_1(s_1 - 1) + c\beta i_0 \mu s_1 - \frac{1}{2}bi_0 s_1 \mu s_1 - \frac{1}{2}bs_1(s_1 - 1)c\beta i_0\Big) \\ &= \nu\Big(\frac{1}{2}bs_1(1 - s_1)c\beta i_0 + \mu i_0 s_1(c\beta - \frac{1}{2}b)\Big). \end{aligned}$$

Thus,

$$\lambda_1\lambda_2 = \frac{1}{2}bs_1(1 - s_1)c\beta i_0 + \mu i_0 s_1(c\beta - \frac{1}{2}b) > 0. \tag{B.5}$$

By (B.4) and (B.5), we conclude that λ_1 and λ_2 have negative real parts and therefore P_2 is locally stable in Γ.

Suppose that P_2 is not globally stable in the interior of Γ. Let $\varphi(t)$ be a solution in the boundary of the basin of attraction of P_2, which intersects the interior of Γ. Since int(Γ) contains no periodic orbits, φ must be a homoclinic orbit or part of a heteroclinic cycle. In either case, φ must limit to an equilibrium which is not P_2. Note that we may assume that $\varphi(t) \in \text{int}(\Gamma)$ for all finite time.

Since P_1 is a hyperbolic saddle and φ is not contained in the stable manifold, φ can not limit to P_1. Near P_0, in the interior of Γ, $i_0' > 0$ and so φ cannot limit to P_0. Hence, φ cannot limit to an equilibrium and so P_2 must be globally stable in int(Γ).

Appendix C

We now substantiate the claim made in equation (8.12), namely,

$$D_+U \leq \left[\frac{i_1'}{i_1} + \xi\frac{s'}{s} - \epsilon\right] U \tag{8.12}$$

where ξ is either 1 or 0, and $\epsilon > 0$.

Proof. Suppose $U = |u_1|$. Then

$$\begin{aligned} D_+|u_1| &\leq \Big[c\beta(2s-1) + 2ki_3 - (2k+g+2b)\Big]|u_1| + \Big[g + ki_2\Big]|u_2| + c\beta s\frac{i_2}{i_1}|u_3| \\ &\leq \Big[c\beta(2s-1) + 2ki_3 - (2k+g+2b)\Big]|u_1| + \Big[g + ki_2\Big]|u_2| \\ &\quad + \Big[c\beta s\frac{i_2}{i_1}\Big](|u_3| + |u_4|) \\ &\leq \Big[c\beta(2s-1) + 2ki_3 - (2k+g+2b) + g + ki_2 + c\beta s\frac{i_2}{i_1}\Big]\, U. \end{aligned} \tag{C.1}$$

Using (8.7) we can write

$$0 = \frac{i_1'}{i_1} - c\beta s - c\beta s\frac{i_2}{i_1} - c\beta s\frac{i_3}{i_1} + (k+b) - g\frac{i_2}{i_1} - ki_3. \tag{C.2}$$

Adding this to (C.1) gives

$$D_+|u_1| \leq \left[\frac{i_1'}{i_1} + c\beta(s-1) + k(i_3 + i_2 - 1) - b - c\beta s\frac{i_3}{i_1} - g\frac{i_2}{i_1}\right] U. \tag{C.3}$$

Suppose $U = |u_2|$. Then

$$D_+|u_2| \leq k|u_1| + \Big[c\beta(2s-1) + 3ki_3 - (2k+g+2b)\Big]|u_2| + \Big|c\beta s + g - ki_1\Big|\frac{i_2}{i_1}|u_3| + ks\frac{i_2}{i_1}|u_4|.$$

Recalling that $c\beta s \geq b$, we see that $g + b \geq k$ implies that $c\beta s + g - ki_1 \geq ks \geq 0$. Therefore

$$\begin{aligned} D_+|u_2| &\leq k|u_1| + \Big[c\beta(2s-1) + 3ki_3 - (2k+g+2b)\Big]|u_2| \\ &\quad + (c\beta s + g - ki_1)\frac{i_2}{i_1}(|u_3| + |u_4|) \\ &\leq \Big[k + c\beta(2s-1) + 3ki_3 - (2k+g+2b) + (c\beta s + g - ki_1)\frac{i_2}{i_1}\Big]U. \end{aligned}$$

Using (C.2), we can rewrite this to get

$$D_+|u_2| \le \Big[\frac{i_1'}{i_1} + c\beta(s-1) + 2ki_3 - (g+b) - ki_2 - c\beta s\frac{i_3}{i_1}\Big]U. \tag{C.4}$$

Next, consider the case where $U = |u_3| + |u_4|$. Then

$$\begin{aligned} D_+\Big(|u_3| + |u_4|\Big) &\le k\frac{i_1}{i_2}|u_2| \\ &\quad + \Big[c\beta(s-1) + 3ki_3 + ki_1 - (2k+2g+2b) \\ &\qquad + \frac{i_1'}{i_1} - \frac{i_2'}{i_2} + \big|c\beta(1-s) - ki_1\big|\Big]|u_3| \\ &\quad + \Big[ks + 3ki_3 + ks - (3k+2g+2b) + \frac{i_1'}{i_1} - \frac{i_2'}{i_2}\Big]|u_4| \\ &\le \Big[k\frac{i_1}{i_2} + \frac{i_1'}{i_1} - \frac{i_2'}{i_2} + 3ki_3 - (2k+2g+2b) \\ &\quad + \max\big\{c\beta(s-1) + ki_1 + \big|cb(1-s) - ki_1\big|, 2ks - k\big\}\Big]U. \end{aligned}$$

Using equation (8.7) we get $\frac{i_2'}{i_2} = k\frac{i_1}{i_2} - (k+g+b) + g\frac{i_3}{i_2} + ki_3$ and so

$$\begin{aligned} &D_+\Big(|u_3| + |u_4|\Big) \\ &\quad \le \Big[\frac{i_1'}{i_1} + 2ki_3 - (k+g+b) - g\frac{i_3}{i_2} \\ &\qquad + \max\big\{c\beta(s-1) + ki_1 + \big|cb(1-s) - ki_1\big|, 2ks - k\big\}\Big]U. \\ &\quad = \max\Big\{\frac{i_1'}{i_1} + c\beta(s-1) + 2ki_3 + ki_1 - (k+g+b) - g\frac{i_3}{i_2} + |c\beta(1-s) - ki_1|, \\ &\qquad \frac{i_1'}{i_1} + 2ki_3 + 2ks - (2k+g+b) - g\frac{i_3}{i_2}\Big\}U. \end{aligned} \tag{C.5}$$

Combining (C.3), (C.4) and (C.5), we see that

$$D_+U \leq \left[\frac{i_1'}{i_1} + \max\Big\{c\beta(s-1) + k(i_3+i_2-1) - b,\right.$$
$$c\beta(s-1) + 2ki_3 - (g+b),$$
$$c\beta(s-1) + 2ki_3 + ki_1 - (k+g+b) + |c\beta(1-s) - ki_1|,$$
$$\left.2ki_3 + 2ks - (2k+g+b)\Big\}\right] U. \tag{C.6}$$

We must now resolve two separate cases. First, consider the case where $k \leq c\beta$. Combining this inequality with the assumption that $k \leq g+b$ we can show that each of the arguments of the maximum in (C.6) must be negative. For the second argument, note that $c\beta(s-1) + 2ki_3 - (g+b) \leq c\beta(s+i_3-1) + ki_3 - k \leq -ks < 0$ since $s \geq \frac{b}{c\beta}$. Each of the other arguments can be similarly bounded away from zero on the negative side. Thus we get

$$D_+U \leq \left[\frac{i_1'}{i_1} - \epsilon_1\right] U \tag{C.7}$$

for some $\epsilon_1 > 0$.

Next, we consider the case where $k \geq c\beta$. By (8.10) we can write

$$0 = \frac{s'}{s} + b(1 - \frac{1}{s}) + c\beta(1-s) - ki_3.$$

Using this, we can rewrite (C.6) as

$$D_+U \leq \left[\frac{i_1'}{i_1} + \frac{s'}{s} + \max\Big\{k(i_2-1) - \frac{b}{s},\right.$$
$$ki_3 - (g+b) + b(1-\frac{1}{s}),$$
$$ki_3 + ki_1 - (k+g+b) + b(1-\frac{1}{s}) + |c\beta(1-s) - ki_1|,$$
$$\left.c\beta(1-s) + ki_3 + 2ks - (2k+g+b) + b(1-\frac{1}{s})\Big\}\right] U. \tag{C.8}$$

Each of the arguments of the maximum in (C.8) can be shown to be bounded away from zero on the negative side, so we have

$$D_+U \leq \left[\frac{i_1'}{i_1} + \frac{s'}{s} - \epsilon_2\right] U \tag{C.9}$$

for some $\epsilon_2 > 0$. Combining (C.7) and (C.9) we have

$$D_+U \leq \left[\frac{i_1'}{i_1} + \xi\frac{s'}{s} - \epsilon\right] U$$

where ξ is either 1 or 0, and $\epsilon > 0$. Thus, the claim made in equation (8.12) is seen to be true. □

Appendix D

We now establish, for $\delta \geq \epsilon + b$, the stability of the matrix M given in (9.3). Recall that

$$M = -\text{diag}\begin{pmatrix} \delta+b+\beta\frac{si}{e}-\epsilon \\ \delta+b+\beta\frac{si}{e} \\ \beta i+\beta\frac{si}{e} \\ \delta+b+\epsilon\frac{e}{i} \\ \beta i+\epsilon\frac{e}{i} \\ \epsilon+b+\epsilon\frac{e}{i} \end{pmatrix} + \begin{bmatrix} 0 & 0 & 0 & -\alpha\beta\frac{si}{e} & 0 & 0 \\ \beta i & 0 & -b & \alpha\beta\frac{si}{e} & 0 & 0 \\ 0 & \delta & 0 & 0 & \alpha\beta\frac{si}{e} & \alpha\beta\frac{si}{e} \\ 0 & \frac{1}{\alpha}\epsilon\frac{e}{i} & 0 & 0 & -b & 0 \\ 0 & 0 & \frac{1}{\alpha}\epsilon\frac{e}{i} & \delta & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta i & 0 \end{bmatrix} \tag{9.3}$$

where α is slightly larger than 1. We consider the differential equation

$$x' = Mx. \tag{D.1}$$

We define a Lyapunov function

$$V = \max\{V_1, V_2\} \tag{D.2}$$

where

$$V_1 = \left\{ \begin{array}{cc} \max\{|x_1|+|x_2|, |x_2|+|x_3|\} & \text{if} \quad \text{sgn}\,(x_1) = \text{sgn}\,(x_2) = \text{sgn}\,(x_3) \\ \max\{|x_1|+|x_2|, |x_3|\} & \text{sgn}\,(x_1) = \text{sgn}\,(x_2) = -\text{sgn}\,(x_3) \\ \max\{|x_1|, |x_2|, |x_3|\} & \text{sgn}\,(x_1) = -\text{sgn}\,(x_2) = \text{sgn}\,(x_3) \\ \max\{|x_1|, |x_2|+|x_3|\} & -\text{sgn}\,(x_1) = \text{sgn}\,(x_2) = \text{sgn}\,(x_3) \end{array} \right\}$$

and

$$V_2 = \left\{ \begin{array}{cc} |x_4|+|x_5|+|x_6| & \text{if} \quad \text{sgn}\,(x_4) = \text{sgn}\,(x_5) = \text{sgn}\,(x_6) \\ \max\{|x_4|+|x_5|, |x_6|\} & \text{sgn}\,(x_4) = \text{sgn}\,(x_5) = -\text{sgn}\,(x_6) \\ \max\{|x_4|+|x_6|, |x_5|\} & \text{sgn}\,(x_4) = -\text{sgn}\,(x_5) = \text{sgn}\,(x_6) \\ \max\{|x_5|+|x_6|, |x_4|\} & -\text{sgn}\,(x_4) = \text{sgn}\,(x_5) = \text{sgn}\,(x_6) \end{array} \right\}.$$

We define V_1 and V_2 to be continuous on the boundaries of the orthants. Using Proposition 2.1, it can be shown that V is a norm on $\mathbb{R}^6$. We now do a case analysis to determine an upper bound on the right-hand derivative D_+V of V. In doing so, it is useful to note that $|x_2|, |x_3|, |x_2+x_3| \leq V_1$ and $|x_4+x_5+x_6|, |x_5+x_6|, |x_4| \leq V_2$.

Case 1. $V_1 > V_2$ and sgn (x_1) = sgn (x_2) = sgn (x_3)

Case 1. A. $|x_1| + |x_2| > |x_2| + |x_3|$

To help with intuition, we think of x_1, x_2 and x_3 as all being positive. The case where they are all negative works exactly the same.

$$\begin{aligned} D_+V &= D_+(|x_1| + |x_2|) \\ &= D_+|x_1 + x_2| \\ &= (\epsilon - \delta - \beta\frac{si}{e})|x_1| - (\delta + b + \beta\frac{si}{e})|x_2| - b|x_3| \\ &\leq (\epsilon - \delta - \beta\frac{si}{e})|x_1| - (\delta + b + \beta\frac{si}{e})|x_2| \\ &\leq (\epsilon - \delta - \beta\frac{si}{e})(|x_1| + |x_2|) \\ &= (\epsilon - \delta - \beta\frac{si}{e})V \end{aligned} \tag{D.3}$$

Case 1. B. $|x_1| + |x_2| < |x_2| + |x_3|$

Note that in this case we can say $\beta i|x_1| < \beta i|x_3|$.

$$\begin{aligned} D_+V &= D_+(|x_2| + |x_3|) \\ &= D_+|x_2 + x_3| \\ &\leq \beta i|x_1| - (b + \beta\frac{si}{e})|x_2| - (b + \beta i + \beta\frac{si}{e})|x_3| + \alpha\beta\frac{si}{e}|x_4 + x_5 + x_6| \\ &\leq -(b + \beta\frac{si}{e})|x_2| - (b + \beta\frac{si}{e})|x_3| + \alpha\beta\frac{si}{e}V_2 \\ &= -(b + \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (-b + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.4}$$

Case 2. $V_1 > V_2$ and sgn (x_1) = sgn (x_2) = $-$sgn (x_3)

As an intuitive aid, we can regard the effect of x_3 having the opposite sign to x_1 and x_2 as being that each of the off-diagonal terms in the third row and

column has the sign flipped. With this augmented matrix, we may then perform the calculations as if we were in the positive octant.

Case 2. A. $|x_1| + |x_2| > |x_3|$

$$\begin{aligned} D_+V &= D_+(|x_1| + |x_2|) \\ &= D_+|x_1 + x_2| \\ &= (\epsilon - \delta - \beta\frac{si}{e})|x_1| - (\delta + b + \beta\frac{si}{e})|x_2| + b|x_3| \\ &< (\epsilon - \delta - \beta\frac{si}{e})|x_1| - (\delta + b + \beta\frac{si}{e})|x_2| + b(|x_1| + |x_2|) \\ &\leq (\epsilon + b - \delta - \beta\frac{si}{e})(|x_1| + |x_2|) \\ &= (\epsilon + b - \delta - \beta\frac{si}{e})V \end{aligned} \tag{D.5}$$

Case 2. B. $|x_1| + |x_2| < |x_3|$

$$\begin{aligned} D_+V &= D_+|x_3| \\ &\leq -\delta|x_2| - (\beta i + \beta\frac{si}{e})|x_3| + \alpha\beta\frac{si}{e}|x_5 + x_6| \\ &\leq -(\beta i + \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (-\beta i + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.6}$$

Case 3. $V_1 > V_2$ and sgn $(x_1) = -\text{sgn}\,(x_2) = \text{sgn}\,(x_3)$

Case 3. A. $|x_1| > |x_2|, |x_3|$

$$\begin{aligned} D_+V &= D_+|x_1| \\ &\leq (\epsilon - \delta - \beta i - \beta\frac{si}{e})|x_1| + \alpha\beta\frac{si}{e}|x_4| \\ &\leq (\epsilon - \delta - \beta i - \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (\epsilon - \delta - \beta i + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.7}$$

Case 3. B. $|x_2| > |x_1|, |x_3|$

$$\begin{aligned} D_+V &= D_+|x_2| \\ &\leq -\beta i|x_1| - (\delta + b + \beta\frac{si}{e})|x_2| + b|x_3| + \alpha\beta\frac{si}{e}|x_4| \\ &< -(\delta + \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (-\delta + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.8}$$

Case 3. C. $|x_3| > |x_1|, |x_2|$

$$\begin{aligned} D_+V &= D_+|x_3| \\ &< -\delta|x_2| - (\beta i\beta\frac{si}{e})|x_3| + \alpha\beta\frac{si}{e}|x_5 + x_6| \\ &\leq -(\beta i\beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (-\beta i + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.9}$$

Case 4. $V_1 > V_2$ and $-\text{sgn}\,(x_1) = \text{sgn}\,(x_2) = \text{sgn}\,(x_3)$

Case 4. A. $|x_1| > |x_2| + |x_3|$

$$\begin{aligned} D_+V &= D_+|x_1| \\ &\leq (\epsilon - \delta - \beta i - \beta\frac{si}{e})|x_1| + \alpha\beta\frac{si}{e}|x_4| \\ &\leq (\epsilon - \delta - \beta i - \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (\epsilon - \delta - \beta i + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.10}$$

Case 4. B. $|x_1| < |x_2| + |x_3|$

$$\begin{aligned} D_+V &= D_+(|x_2| + |x_3|) \\ &= D_+|x_2 + x_3| \\ &\leq -\beta i|x_1| - (b + \beta\frac{si}{e})|x_2| - (b + \beta i + \beta\frac{si}{e})|x_3| + \alpha\beta\frac{si}{e}|x_4 + x_5 + x_6| \\ &\leq -(b + \beta\frac{si}{e})V_1 + \alpha\beta\frac{si}{e}V_2 \\ &< (-b + (\alpha - 1)\beta\frac{si}{e})V \end{aligned} \tag{D.11}$$

Case 5. $V_1 < V_2$ and sgn (x_4) = sgn (x_5) = sgn (x_6)

$$\begin{aligned} D_+V &= D_+(|x_4| + |x_5| + |x_6|) \\ &= D_+(|x_4 + x_5 + x_6|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_2 + x_3| - (b + \epsilon\frac{e}{i})|x_4| - (b + \epsilon\frac{e}{i})|x_5| - (\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (b + \epsilon\frac{e}{i})V_2 \\ &< -bV \end{aligned} \tag{D.12}$$

Case 6. $V_1 < V_2$ and sgn (x_4) = sgn (x_5) = $-$sgn (x_6)

Case 6. A. $|x_4| + |x_5| > |x_6|$

$$\begin{aligned} D_+V &= D_+(|x_4| + |x_5|) \\ &= D_+(|x_4 + x_5|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_2 + x_3| - (b + \epsilon\frac{e}{i})|x_4| - (b + \beta i + \epsilon\frac{e}{i})|x_5| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (b + \epsilon\frac{e}{i})V_2 \\ &< -bV \end{aligned} \tag{D.13}$$

Case 6. B. $|x_4| + |x_5| < |x_6|$

$$\begin{aligned} D_+V &= D_+(|x_6|) \\ &= -\beta i|x_5| - (\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &\leq -(\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &= -(\epsilon + b + \epsilon\frac{e}{i})V \end{aligned} \tag{D.14}$$

Case 7. $V_1 < V_2$ and $\text{sgn}\ (x_4) = -\text{sgn}\ (x_5) = \text{sgn}\ (x_6)$

Case 7. A. $|x_4| + |x_6| > |x_5|$

$$\begin{aligned} D_+V &= D_+(|x_4| + |x_6|) \\ &= D_+(|x_4 + x_6|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_2| - (\delta + b + \epsilon\frac{e}{i})|x_4| + (b - \beta i)|x_5| - (\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_2| - (\delta + b + \epsilon\frac{e}{i})|x_4| + b(|x_4| + |x_6|) - (\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (\min\{\delta, \epsilon\} + \epsilon\frac{e}{i})(|x_4| + |x_5|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (\min\{\delta, \epsilon\} + \epsilon\frac{e}{i})V_2 \\ &< -\min\{\delta, \epsilon\}V \end{aligned} \tag{D.15}$$

Case 7. B. $|x_4| + |x_6| < |x_5|$

$$\begin{aligned} D_+V &= D_+(|x_5|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_3| - \delta|x_4| - (\beta i + \epsilon\frac{e}{i})|x_5| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (\beta i + \epsilon\frac{e}{i})V_2 \\ &< -(\beta i + \epsilon\frac{e}{i})V \end{aligned} \tag{D.16}$$

Case 8. $V_1 < V_2$ and $-\text{sgn}\ (x_4) = \text{sgn}\ (x_5) = \text{sgn}\ (x_6)$

Case 8. A. $|x_5| + |x_6| > |x_4|$

$$\begin{aligned} D_+V &= D_+(|x_5| + |x_6|) \\ &= D_+(|x_5 + x_6|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_3| - \delta|x_4| - \epsilon\frac{e}{i}|x_5| - (\epsilon + b + \epsilon\frac{e}{i})|x_6| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_3| - \epsilon\frac{e}{i}(|x_5| + |x_6|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - \epsilon\frac{e}{i}V_2 \\ &< (\frac{1}{\alpha} - 1)\epsilon\frac{e}{i}V \end{aligned} \tag{D.17}$$

Case 8. B. $|x_5| + |x_6| < |x_4|$

$$\begin{aligned} D_+V &= D_+(|x_4|) \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}|x_2| - (\delta + b + \epsilon\frac{e}{i})|x_4| + b|x_5| \\ &\leq \frac{1}{\alpha}\epsilon\frac{e}{i}V_1 - (\delta + \epsilon\frac{e}{i})V_2 \\ &< -\delta V \end{aligned} \tag{D.18}$$

By combining equations D.3-D.18, we see that if $\delta \geq \epsilon + b$ then it is possible to choose α which is greater than, but sufficiently close to, one so that $D_+V < 0$ on K. Let μ be the Lozinskii measure induced by V. Then equation (2.3) implies $\mu(M) < 0$ on K.